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**FREEDOM OF INFORMATION ACT REQUEST**

**VIA FEDEX AND EMAIL** June 11, 2018

Mr. Gorka Garcia-Malene
Freedom of Information Act Officer
National Institutes of Health
Building 31 Room 5B35
9000 Rockville Pike
Bethesda, Maryland 20892
Email: nihfoia@mail.nih.gov

Re: Task Force on Safer Childhood Vaccines, Chaired by the Director of NIH (IR#0030)

Dear Mr. Garcia-Malene:

This firm represents Informed Consent Action Network ("ICAN"). On behalf of ICAN, we are requesting records pursuant to the Freedom of Information Act (5 U.S.C. § 552, as amended) from the files of the National Institutes of Health ("NIH").

Section 300aa-27(a) of Title 42 of the United States Code provides that "the Secretary shall--(1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on the effective date of this part [effective Dec. 22, 1987] and promote the refinement of such vaccines, and (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines."

Section 300aa-27(b) of Title 42 of the United States Code provides that "The Secretary shall establish a task force on safer childhood vaccines which shall consist of the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Director of the Centers for Disease Control" (the "**Task Force on Safer Childhood Vaccines**"). This section further provides that "The Director of the National Institutes of Health shall serve as chairman of the task force" and that "the task force shall prepare recommendations to the Secretary concerning implementation of the requirements of subsection (a) of this section."

By this letter, please provide the following records, created on or after December 22, 1987, in NIH's possession to the above referenced address in electronic form on a CD or DVD:

**Any and all recommendations made by the Task Force on Safer Childhood Vaccines established pursuant to 42 U.S.C. § 300aa-27(b).**

We ask that you waive any and all fees or charges pursuant to 5 U.S.C. § 552 (a)(4)(A)(iii). ICAN is a not-for-profit 501(c)(3) organization whose mission is to raise public awareness about vaccine safety and to provide the public with information to give informed consent. As part of their mission, ICAN actively investigates and disseminates information regarding vaccine safety issues, including through their website, and through press events and releases. They are seeking the information in this FOIA request to allow them to contribute to the public understanding of the government's vaccine safety programs, including the government's efforts to promote vaccine safety. The information we are requesting will not contribute to any commercial activities.

Please note that the FOIA provides that if only portions of a requested file are exempted from release, the remainder must still be released. We therefore request that we be provided with all non-exempt portions which are reasonably segregable. We further request that you describe any deleted or withheld material in detail and specify the statutory basis for the denial as well as your reasons for believing that the alleged statutory justification applies. Please also separately state your reasons for not invoking your discretionary powers to release the requested documents in the public interest. Such statements may help to avoid unnecessary appeal and litigation. ICAN of course reserves all rights to appeal the withholding or deletion of any information.

Access to the requested records should be granted within twenty (20) business days from the date of your receipt of this letter. Failure to respond in a timely manner shall be viewed as a denial of this request and ICAN may immediately file an administrative appeal.

If you would like to discuss our requests or any issues raised in this letter, please feel free to contact me at (212) 532-1091 during normal business hours. Thank you for your time and attention to this matter.

Very truly yours,

Aaron Siri, Esq.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Freedom of Information Office
Building 31, Room 5B-35
31 Center Drive, MSC 2107
Bethesda, Maryland 20892-2107
phone: (301) 496-5633
fax: (301) 402-454

January 31, 2020

Aaron Siri, Esq.
Siri & Glimstad LLP
200 Park Avenue
Seventeenth Floor
New York, NY 10166

Re: NIH FOI Case No. 48013

Dear Mr. Siri:

This is the final response to your June 11, 2018, Freedom of Information Act (FOIA) request addressed to the National Institutes of Health (NIH) FOIA office. Department of Health and Human Services' (HHS) policy calls for the fullest possible disclosure provided by the FOIA, 5 U.S.C. §552, consistent with the protections contained therein. The implementing HHS Regulations establish the criteria pursuant to which the FOIA is administered, *see* 45 C.F.R. Part 5. Copies of the FOIA and the HHS FOIA Regulations are located at: http://www.nih.gov/icd/od/foia/efoia.htm and http://www.nih.gov/icd/od/foia/cfr45.htm.

On behalf of Informed Consent Action Network, you requested any and all recommendations made by the Task Force on Safer Childhood Vaccines established pursuant to 42 U.S.C. § 300aa-27(b) that were created on or after December 22, 1987.

The Office of the Director, Executive Secretariat searched their files and found the enclosed 93 pages. The information being withheld is protected from release pursuant to Exemption 5 of the FOIA, 5 U.S.C. § 552 (b)(5); and section 5.31(e) of the HHS FOIA Regulations, 45 CFR Part 5. Exemption 5 permits the withholding of internal government records which are pre-decisional and contain staff advice, opinion, and recommendations. This exemption is intended to preserve free and candid internal dialogue leading to decision-making.

You have the right to appeal this determination to deny you access to information in the Agency's possession. Should you wish to do so, your appeal must be sent within ninety (90) days of the date of this letter, following the procedures outlined in Subpart F of the HHS FOIA Regulations (https://www.federalregister.gov/documents/2016/10/28/2016-25684/freedom-of-information-regulations) to:

Assistant Secretary for Public Affairs
Agency Chief FOIA Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs

Room 729H
200 Independence Avenue, S.W.
Washington, DC 20201

Clearly mark both the envelope and your letter "Freedom of Information Act Appeal."

If you are not satisfied with the processing and handling of this request you may contact the NIH FOIA Public Liaison and/or the Office of Government Information Services (OGIS):

| NIH FOIA Public Liaison | OGIS |
|---|---|
| Stephanie Clipper | National Archives and Records Admin. |
| Public Affairs Specialist | 8601 Adelphi Rd – OGIS |
| Office of Communications and Public Liaison | College Park, MD 20740-6001 |
| Building 1, Room 131 | 202-741-5770 (phone) |
| 1 Center Drive | 1-877-684-6448 (toll-free) |
| Bethesda, MD 20814 | 202-741-5769 (fax) |
| 301-496-2411 (phone) | ogis@nara.gov (email) |
| nihfoia@mail.nih.gov (email) | |

In certain circumstances provisions of the FOIA and Department of Health and Human Services FOIA Regulations allow us to recover part of the cost of responding to your request. Because no unusual circumstances apply to the processing of your request, there are no charges associated with our response.

If you have any questions about this response, please call 301-496-5633.

Sincerely,

Gorka Garcia-Malene
Freedom of Information Officer, NIH

Enclosures: 93 pages

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

MAR 15 1990

TO: Acting Director, NIH
Acting Commissioner, FDA
Director, CDC

FROM: Assistant Secretary for Health
and Director, National Vaccine Program

SUBJECT: Establishment of a Task Force on Safer Childhood Vaccines

Pursuant to Section 6601 of the Omnibus Budget Reconciliation Act of 1989, P.L. 101-239, which extensively amends Subtitle 2 (the National Vaccine Injury Compensation Program) of Title XXI (Vaccines) of the Public Health Service Act:

- The Secretary shall establish a task force on safer childhood vaccines which shall consist of the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Director of the Centers for Disease Control;

- The Director of the National Institutes of Health shall serve as chairman of the task force; and

- In consultation with the Advisory Commission on Childhood Vaccines, the task force shall prepare recommendations to the Secretary concerning implementation of the requirements Section 2127, Mandate for Safer Childhood Vaccines, of the PHS Act.

Under the authority delegated to me, I hereby establish the Task Force on Safer Vaccines. So that preparation of recommendations concerning implementation of Section 2127 may begin, please advise Dr. Kenneth Bart, the Deputy Director of the National Vaccine Program, whether you or your designated alternate will represent your agency on the task force. Please provide the name and phone number of your representative by March 20 to the National Vaccine Program Office, Room 13A-53 Parklawn (443-0715).

James O. Mason

James O. Mason, M.D., Dr.P.H.

cc: Administrator, HRSA

MAR 15

82415

OD CENTRAL FILE CLASS. NO. RES 18

March 27, 1990

NOTE TO KAREN O'STEEN

Re: Establishment of a Task Force on Safer Childhood Vaccines
NIH Exec. Sec,. #82415

In response to Dr. Mason's request for an NIH representative to chair the Task Force on Safer Childhood Vaccines, the NIAID would like to designate Dr. John La Montagne. Dr. La Montagne is currently the NIH representative to the National Vaccine Program and is responsible for vaccine development [excluding AIDS] within the NIAID.

I have contacted the National Vaccine Program Office [Dan Lahn] and provided Dr. La Montagne's name as the NIH designate. Dr. La Montagne will speak with Dr. Bart regarding the responsibilities associated with chairing the Task Force and will keep Dr. Raub informed as he does for other National Vaccine Program activities.

Diane

Diane Shartsis Wax

cc: Dr. La Montagne

82630

OD CENTRAL FILE CLASS. NO.

NIH

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

RECEIVED
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EXECUTIVE SECRETARIAT

JUN 2 1 1996

To: The Secretary

Through: DS ICT 12/31
COS IBC 12/31
ES

From: Director, NIH

Subject: Final Report and Recommendations of the Task Force on Safer Childhood Vaccines--ACTION

## BACKGROUND

Section 2127 ( c ) of the Public Health Service (PHS) Act [42 USC (33aa-27)], as amended in 1987, requires that a Task Force on Safer Childhood Vaccines (TFSCV, or the Task Force) be established by the Secretary of Health and Human Services to examine the safety of vaccines and to make recommendations to the Secretary that wi ensure the development of safer childhood vaccines and improve the "licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, recall of reactogenic lots or batches (of vaccines), and research on vaccines." The Task Force consisted of representatives from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the National Vaccine Injury Compensation Program (NVICP), the Office of General Counsel (OGC), and the National Vaccine Program Office (NVPO).

The attached report summarizes the final recommendations of the Task Force.

## HIGHLIGHTS

The recommendations of the Task Force span the breadth of activities and responsible agencies required to ensure the safety of vaccines. These are summarized in the following four general recommendations:

(1) Assess and address national concerns about the risks and benefits of vaccines to enhance the education of individuals, families, and health care professionals.

(2) Strengthen the national capability to conduct the research and development needed to promote the licensure of safer vaccines.

7/1/2017
150940

(3) Strengthen the national capability to conduct surveillance of vaccine-preventable diseases and to evaluate potential adverse events and vaccine efficacy.

(4) Charge the Interagency Vaccine Group (IAVG), composed of representatives from those agencies involved in vaccine research, development, evaluation, regulation, and immunization, with the ongoing responsibility to ensure that the appropriate vaccine safety activities are carried out. The IAVG would be expected to seek routine technical consultation from an expert external advisory body.

Upon your review and approval, the Report will be distributed to a number of audiences within Congress, the Federal Government, the medical and research communities, and the public.

RECOMMENDATION

I recommend that you review and approve the attached report.

Harold Varmus

Harold Varmus, M.D.

Attachments:
Executive Summary
Task Force on Safer Childhood Vaccines: Final Report and Recommendations

DECISION

Approved _____ Disapproved _____ Date JAN 3 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

**MEMORANDUM**

**DATE:** June 11, 1996

**FROM:** Director, National Institute of Allergy and Infectious Diseases

**SUBJECT:** Approval and Transmission of the Final Report and Recommendations of the Task Force on Safer Childhood Vaccines

**TO:** Director, NIH

The Task Force on Safer Childhood Vaccines, created by Congress under Section 2127 ( c )of the Public Health Act as amended in 1987, is required to write and submit to the Secretary, HHS, a Final Report. As required, ten Copies of *Task Force on Safer Childhood Vaccines: Final Report and Recommendations*, are attached for submission.

Anthony S. Fauci, M.D.

JUN 20 12 21 '96

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# *TASK FORCE ON SAFER CHILDHOOD VACCINES*

## *FINAL REPORT and RECOMMENDATIONS*

*April 19, 1996*

# TASK FORCE ON SAFER CHILDHOOD VACCINES
# FINAL REPORT and RECOMMENDATIONS

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## TASK FORCE ON SAFER CHILDHOOD VACCINES
## FINAL REPORT and RECOMMENDATIONS

### PREFACE

This report represents the distillation of evaluation and discussions by a group of public health experts on the topic of vaccine safety. The broad scope of the congressionally-mandated charge forced an equally broad analysis in execution, congruent with other congressionally-mandated actions focused on discrete components of the vaccine safety network in the United States. The Task Force recommendations reflect a consensus on how to continue, and indeed, improve, the diverse set of activities and responsibilities related to vaccine safety.

The recommendations clearly acknowledge that vaccine safety depends on a complex network of activities, and that the modern tools of immunology, molecular biology and epidemiology offer the potential for prevention of additional diseases by the development of vaccines, as well as the assurance of their safety. This report and recommendations propose that additional progress in vaccine safety can be anticipated, and chart a course to assure that this is continued to the benefit of the Nation's children.

John R. La Montagne, Ph.D.
Chair
Task Force on Safer Childhood Vaccines
Director, Division of Microbiology and
Infectious Diseases
National Institute of Allergy and
Infectious Diseases
National Institutes of Health

## TASK FORCE ON SAFER CHILDHOOD VACCINES
## FINAL REPORT and RECOMMENDATIONS
## Acknowledgments

This report is the result of discussions held by members of the Public Health Service over the past four years. The Task Force wishes to acknowledge the contributions of all participants in the difficult and complex task of examining the existing U.S. system for assuring the safety of childhood vaccines at a time of enormous change.

NIH:
Dr. John R. La Montagne, Chair, TFSCV.
Dr. Regina Rabinovich
Dr. George Curlin
Dr. Chris Breyer
Dr. Bruce Gellin

CDC:
Dr. Walter Orenstein
Dr. Robert Chen
Dr. Stephen Hadler
Dr. Steven Wassilak
Dr. Roger Bernier
Dr. John Glasser
Mr. Stephen Sepe

FDA:
Dr. Carolyn Hardegree
Dr. Elaine Esber
Dr. Susan Ellenberg
Mr. William Stevens
Ms. Karen Chaitkin
Dr. Suresh Rastogi
Dr. Jerome Donlon

NVICP:
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Dr. Marie Mann
Mr. Thomas Balbier
Dr. Robert Weibel

NVPO:
Dr. Ken Bart
Dr. Yuth Nimit
Dr. Kimi Lin
Dr. Peter Patriarca
Ms. Cathy Michaelosky
Dr. Anthony Robbins
Dr. Roy Widdus

OGC:
Mr. David Benor
Ms. Gemma Flamberg

## GLOSSARY

AAP: American Academy of Pediatrics

AAFP: American Academy of Family Practitioners

ACCV: Advisory Commission on Childhood Vaccines

ACIP: Advisory Committee on Immunization Practices

Adverse Event: Negative sequelae, of variable severity, which occurs after an intervention, but may or may or may not be caused by the intervention.

Adverse Reaction: Negative sequelae caused by an intervention; these can be minor (pain, swelling, low-grade fever), severe (requiring hospitalization), or lethal (causing death).

CDC: Centers for Disease Control and Prevention

CVI: Children's Vaccine Initiative

DoD: Department of Defense

EPI: Expanded Programme on Immunization - WHO

FDA: Food and Drug Administration

GLP: Good Laboratory Practices

GPV: Global Programme on Vaccines and Immunization - WHO

GMP: Good Manufacturing Practices

LLDB: Large-linked Databases

NIH: National Institutes of Health

NVAC: National Vaccine Advisory Committee

PHS: Public Health Service

Safety: "the relative freedom from harmful effect to the persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." (21 CFR 600.3 (p))."

Task Force on Safer Childhood Vaccines (TFSCV) (The Task Force)

Vaccine lot: "that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel" (21 CFR 600-639).

Vaccine: A preparation that is administered to produce or artificially increase immunity to a particular disease.

VAERS: Vaccine Adverse Events Reporting System

VRBPAC: Vaccines and Related Biologicals Products Advisory Committee to the FDA.

WHO: World Health Organization

## TASK FORCE ON SAFER CHILDHOOD VACCINES
## FINAL REPORT and RECOMMENDATIONS

### Executive Summary

As we prepare to enter the 21st century, the promise of vaccines has never been greater. If this promise is to be fully realized, the vaccines we use must not only be effective in the prevention of diseases, they must also be safe. Recent reviews by the Institute of Medicine (IOM) have identified many gaps and limitations, however, in current knowledge about the safety of vaccines. The Task Force on Safer Childhood Vaccines (TFSCV, or the Task Force) was established by the Secretary at the direction of Congress, with the sole purpose of examining the safety of vaccines and making recommendations to the Secretary, Health and Human Services, that will assure the development of safer childhood vaccines, and improve the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, recall of reactogenic lots or batches, and research on vaccines. This report summarizes the findings and recommendations of the Task Force.

The Task Force was constituted of representatives from several Public Health Service (PHS) agencies: the National Institutes of Health (NIH), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Vaccine Injury Compensation Program (NVICP), the Office of General Counsel (OGC) and the National Vaccine Program Office (NVPO). As with any committee activity, a number of individuals have participated in discussions that resulted in the creation of this report (see acknowledgements).

There are many reasons that this is a critical task and therefore was mandated by law, but several were emphasized by the Task Force. The first is a paradox inherent in the very success of vaccines and immunization programs. Concerns about vaccine safety become increasingly prominent when effective use of vaccines in a population reduces the incidence of the target diseases. Yet, since few diseases are eradicable, only immunization programs which maintain public confidence in vaccines can prevent tragic recurrence of disease, as demonstrated by outbreaks of pertussis in several countries during the 1980's. The second reason is that even under conditions of epidemic or endemic transmission, there is a probability that any given individual in the population will escape infection and disease. This consideration brings into focus the two reasons for using vaccines - to protect an individual from infection (individual health) and to protect the population from the spread of disease (public health). Also, vaccines, unlike therapeutic interventions, are given to healthy individuals. Consequently the risks associated with any vaccine must be minimal and vaccines must be extraordinarily safe.

Since 1990, the PHS has made significant progress in creating much of the infrastructure necessary to ameliorate the gaps identified by the IOM. This process is incomplete, however. Advances in basic biomedical research and the accelerating pace of the revolution in biotechnology make possible a large array of new vaccines in the future. At the same time, safety issues regarding already-licensed vaccines have become of paramount importance to the success and stability of immunization programs, vaccine companies, and public support for these activities. The continued improvement and assurance of vaccine safety is as much a research priority as the development of vaccines for the diseases that continue to affect mankind.

The recommendations of the Task Force arise from the broad review and evaluation presented in this report, and span the breadth of activities and responsible Agencies required to assure the safety of vaccines. These are summarized in the following four general recommendations:

1. ***Assess and address national concerns about the risks and benefits of vaccines to enhance the education of the public, families, and health care professionals.***

As the struggle against disease with vaccines progresses, the assessment of risks and benefits of this intervention has changed, as few health care providers or parents may have seen a case of vaccine-preventable diseases. We need to know more about how to communicate what is known and what is not known about true and perceived risk. Furthermore, it is extraordinarily difficult to obtain spontaneous reporting of adverse events after immunization without a presumption of potential causality. Education must appropriately target the public, families and health care professionals in order to assure optimal prevention with vaccines.

2. ***Strengthen the national capability to conduct research, development needed to promote the licensure of safer vaccines.***

Vaccine research and development is driven by both the push of scientific advances as well as the pull from the need to control and prevent disease. When an effective and safe vaccine is available, the perception or association of true adverse events must be high indeed to support the costly development (approximately $200 Million) for a "safer" vaccine. Technological barriers confound this sequence of events. For example, the development of recombinant hepatitis B vaccines, which did not confer the potential risk of transmission of other infections, was accomplished less than a decade after the licensure of serum derived vaccine. However, the development of safer acellular pertussis vaccines, a complex task which has required new technologies not available 10 years ago, has been a much slower process.

3. ***Strengthen the national capability to conduct surveillance of vaccine preventable diseases, and to evaluate potential adverse events and vaccine efficacy.***

The safe use of a vaccine to control disease requires continuous monitoring for the disease as well as for known and potential adverse events following vaccine administration. This type of information makes it possible to answer vital public health questions: Is the disease effectively controlled, or has something (the vaccine, the human host or the environment) changed? Has the risk/benefit evaluation altered? Does the use or composition of the vaccine need to be modified in response to different conditions? Are changes in national immunization policies regarding mandated childhood vaccines warranted?

Historically, for both methodologic and logistical reasons, it has been difficult to maintain effective surveillnace for adverse events post licensure. Since 1990, the PHS has initiated major improvement in its ability to conduct both passive and active surveillance for adverse events. Continued support for these projects are critical to assuring adequate monitoring of the present and future safety of vaccines in the U.S.

4. ***The Task Force recommends that the Interagency Vaccine Group, comprised of representatives from those agencies involved in vaccine research, development, evaluation, regulation and immunization activities, be charged with the ongoing responsibility to assure that appropriate vaccine safety activities are carried out. The IAVG would be expected to seek routine technical consultation from an expert external advisory body.***

The Task Force identified the roles and responsibilities of the federal agencies, vaccine companies, health care providers, research community and parents in assuring that vaccines are safe. Experience over the past century teaches that the activities of each of

these are linked to the activities of the others, making both coordination and communication essential to vaccine safety. Furthermore, the group charged with this process must be able to focus on safety.

Unless eradication of a disease is achieved, the Task Force is committed to the concept that the public health is best served by the continued pursuit of safer and more effective vaccines, and by optimizing the safe use of existing vaccines through improvements in the immunization schedule and delivery of vaccines. The recommendations presented in this report are congruent with the Nation's immunization and vaccine goals presented in the U.S. National Vaccine Plan in 1994.

## INTRODUCTION

Vaccines and immunization programs have been so remarkably successful in eliminating or controlling many of the more common infectious diseases of childhood that their use is often taken for granted. Their impact is evident everyday and everywhere in the United States. Cases of diphtheria, whooping cough (pertussis), tetanus, measles, mumps and German measles (rubella) are so unusual in the United States that these infections and their consequences are unknown to most Americans. Just a generation ago, the coming of summer brought fears of epidemics of polio; now iron lungs can only be seen in museums and dusty hospital storerooms. This has been accomplished through the development and use of safe and effective vaccines in national immunization programs around the world. Smallpox was eradicated from the planet in 1977. Polio eradication was defined as a goal for the year 2000. Remarkably, the Americas were declared to be free of wild-virus poliomyelitis on September 29, 1994, with the last recorded case of wild-type disease registered in South America in 1991. Efforts in Asia and the Pacific are well underway.

The global use of vaccines to control childhood infections has never been broader. The progress of the Expanded Program of Immunization (EPI) of the World Health Organization has proceeded to the point that it is now estimated that 80% of the world's children are immunized to protect them against pertussis, diphtheria, tuberculosis, polio, tetanus, and measles. Indeed, vaccines offer solutions to our most common infectious diseases, and have become part of the background of everyday life.

Before the development of the vaccines commonly used today, infectious diseases were the most common cause of death, disability and disease in the United States. Lives were shortened or

**TABLE 1.**
**Comparison of Maximum and Current Reported Morbidity**
**Vaccine-Preventable Diseases , U.S.**

| Disease | Maximum Reported Cases | Year Maximum reported | Reported Cases 1995 (provisional) | Percent Change |
|---|---|---|---|---|
| Diphtheria | 206,939 | 1921 | 0 | - 99.99 |
| Measles | 894,134 | 1941 | 288 | - 99.97 |
| Mumps | 152,209 | 1968 | 840 | - 99.45 |
| Pertussis | 265,269 | 1934 | 4,315 | - 98.37 |
| Polio (wild) | 21,269 | 1952 | 0 | -100.00 |
| Rubella | 57,686 | 1969 | 200 | - 99.65 |
| Congenital Rubella Syndrome | 20,000 (est) | 1964-5 | 7 | - 99.96 |
| Tetanus | 1,560 | 1948 | 34 | - 97.82 |
| *Haemophilus influenza* invasive disease | 20,000 | 1984 | 1,164 | - 94.18 |

devastated by polio, pertussis, measles and diphtheria (Table 1). Severe, life-long complications of these infections were commonplace. Permanent paralysis often followed polio virus infection. Deafness and blindness were known risks after measles infection. Whooping cough left survivors with permanent brain damage. However, the control over infectious diseases that we now enjoy because of the availability of effective vaccines creates a new and difficult problem. Simply stated, as disease control is firmly established and the infections recede in importance, the adverse events associated with the use of vaccines become more evident and gain in importance; their risk-to-benefit relationship is altered. In 1995, for example, the number of reports to the Vaccine Adverse Event Reporting System was almost double the sum of the vaccine-preventable diseases reported (Table 1).

Medical interventions and public health measures, including vaccines, are used because they are expected to produce tangible benefits. However, the benefits are associated with the risk of an **adverse reaction** (caused by the intervention) or an **adverse event** (may or may not be caused by the intervention), perhaps even a lethal one. Many vaccines induce short-lived periods of fever, pain, soreness at the injection site, malaise or other constitutional manifestations. Rarely, more serious reactions may occur. Individuals with unrecognized allergies to eggs, for example, may develop an anaphylactic reaction to egg proteins that might be present in some vaccines. Individuals with unrecognized immunodeficiencies may develop serious and perhaps fatal complications when they receive a vaccine containing an attenuated, living organism (e.g., vaccinia virus in the smallpox vaccine or an attenuated polio virus in the oral polio vaccine). As disease control is established, these adverse events or reactions increase in importance. All adverse events must be considered with great care since they may alter the balance of risk versus benefit.

Safety is not a condition that can be absolutely guaranteed. As defined in the biologics regulation, it is "the relative freedom from harmful effect to the persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." (21 CFR 600.3 (p)).

As a result of the process in place for the development, testing and licensure of new vaccines, severe adverse events (those requiring hospitalization, causing chronic medical conditions, or resulting in death) are rare, or else would constitute an impediment to vaccine licensure. Severe adverse events must be considered in relationship to the benefit the vaccines produce for the individual and also for the society. This risk- to-benefit relationship is a more complex one when applied to vaccines than to therapeutic or surgical interventions for many reasons, but primarily due to the following:

- Vaccines are given to persons presumed to be healthy, usually infants and children.
- Vaccines protect the individual from a statistically predictable exposure to the vaccine-prevented infection, not a current medical problem.[2]
- Vaccines reduce or eliminate the burden of disease in the general population, by reducing spread of disease. Vaccines are sometimes given to a large proportion of individuals to also protect the entire population.
- Vaccines are often used in campaigns to control epidemic or endemic public health problems - and thus the risk-to-benefit ratio is applied to the general population.
- Vaccines are often legally required or mandated by states to protect the health of the general population.

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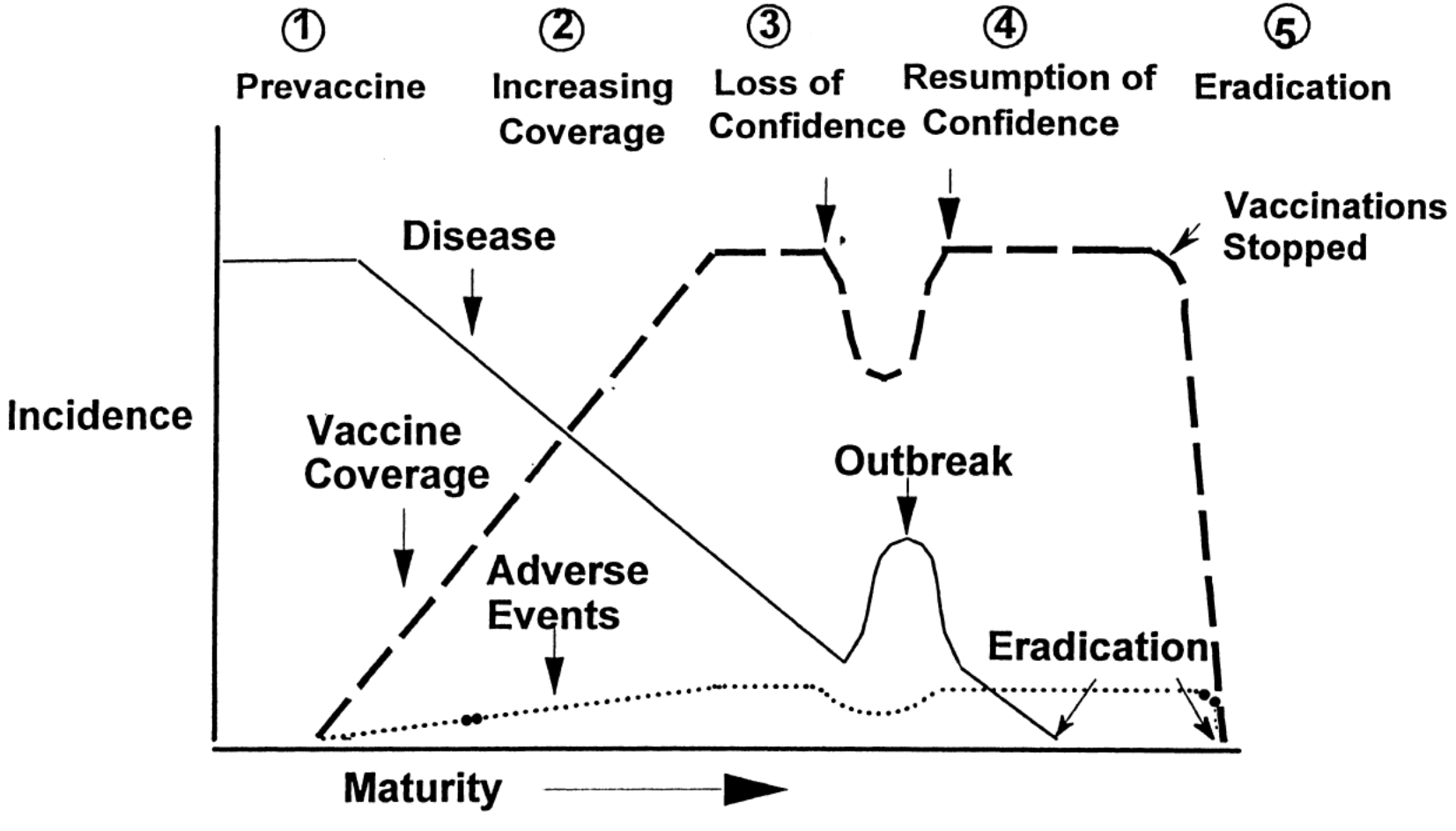
[2] There are exceptions. For example, BCG vaccine is now used in the therapy of bladder cancer.

# Evolution of Immunization Program and Prominence of Vaccine Safety



The dynamic nature of the assessment of the benefits and risks associated with any vaccine varies with vaccine coverage, disease incidence and the specific adverse events (Chen, 1994). A few discrete stages, illustrated in Figure 1, can be described:

Stage 1: In the prevaccine era, morbidity and/or mortality due to the disease are high, and for this reason a vaccine is developed.

Stage 2: An effective vaccine results in less disease. With progressive increases in the vaccination levels of the population immunity in most of the population is derived from vaccination rather than from disease. A true vaccine adverse reaction, even if extremely rare, will be observed more "frequently" as vaccine is used in millions of people .

Stage 3: Over time the threat of the disease will be less urgently perceived, and reports of adverse events will increase (as the vaccine is used in larger populations) and receive greater attention. The adverse events may be attributed to vaccination by the public even though scientific evidence of causation other than temporal association may be lacking. Such temporal associations are especially difficult to dissect with medical events for which etiology remains unknown, such as sudden infant death syndrome (SIDS), and may lead to erosion of confidence in the vaccine, reduction of vaccine usage, and a resurgence of disease.

Stage 4: The cyclical resurgence of disease or the availability of an alternative vaccine may boost public acceptance of vaccination against the disease, resulting in the high vaccination levels and the reduction of disease. For some vaccine-preventable diseases (e.g., smallpox), the epidemiologic characteristics may permit the eradication of the causative organism and hence the disease from mankind.

Stage 5: Once eradication is certified, vaccine use can be stopped, thereby eliminating the adverse reactions. For diseases with lower transmissibility or for which effective therapies exist, routine vaccinations may be stopped in some areas before global eradication is confirmed. This occurred with the use of smallpox vaccine in the US (MMWR, 1971) and BCG vaccine in Sweden (Romanus, 1987). Similarly, the use of oral live attenuated polio vaccine (OPV) is being debated by advisory bodies in the U.S., in the face of regional elimination of polio in the Americas.

Although not all of the above stages are applicable to the use of every vaccine (for example, not all diseases are eradicable), this concept of "stages" illustrates, in a simple way, the the dynamic nature of the vaccine-risk trade-offs which was considered as a framework in the discussions of the Task Force.

## TASK FORCE ON SAFER CHILDHOOD VACCINES (TFSCV): THE LEGAL FRAMEWORK

The Task Force on Safer Childhood Vaccines (TFSCV) was mandated by Congress in 1986 as part of a set of statutes which have fundamentally impacted on the national childhood immunization system of administration, record keeping and reporting, compensation for vaccine injuries, labeling, coordination of these responsibilities, and education. Enacted from 1986 through 1989, these have served to accelerate or initiate a number of concurrent activities throughout the Public Health Service. Appendix 2 contains the details of the vaccine legislation from Public Law 99-660, known as the National Childhood Vaccine Injury Act (NCVIA), which enacted Title XXI of the Public Health Service Act in 1986.

The NCVIA established the National Vaccine Program, whose goal is "to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against

adverse reactions to vaccines". Amendments to the Act in 1987 established the National Vaccine Injury Compensation Program (NVICP) and other required activities. These included:

- Section 2125, "Recording and Reporting of Information" defined the information required to be recorded for the administration of vaccines by every health care provider in the U.S.;

- Section 2126 required the Secretary to develop Vaccine Information Materials for vaccines subject to the NVICP;

- Section 2128, "Manufacturer Recordkeeping and Reporting;"

- Section 2127, "Mandate for Safer Childhood Vaccines" became effective on December 22, 1987 and required a report on the progress of the issues included in Section 2127(a) (development of safer childhood vaccines; the licensing, manufacturing, processing, testing, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, recall of reactogenic lots, and research on vaccines). Paragraph (b), which calls for the establishment of the **Task Force on Safer Childhood Vaccines**, was not enacted until December 1989 (Public Law 101-239) (Box 1).

- Section 312 - Required a review of adverse events associated with pertussis and rubella vaccines;

- Section 313 - Required a review of adverse events associated with other childhood vaccines;

- Section 314 - Required a review of labeling for warnings, use instructions, and precautionary information.

**Reporting requirements**

The TFSCV is required to prepare a report and recommendations for the Secretary, DHHS, in consultation with the Advisory Commission on Childhood Vaccines (ACCV), an external advisory group charged with providing advice to the Secretary on the operation of the National Vaccine Injury Compensation Program (NVICP). The report of the Task Force must include recommendations on how to "promote the development...and make or assure improvements" as described in Section 2127 (a). In its development, the Task Force reviewed and found it compatible with the aims of the National Vaccine Plan (PHS, 1994) to ensure the promotion of vaccine safety and effectiveness. This document constitutes the report of the Task Force.

Section 2127 of the Act embodies the most explicit language regarding safety, as well as the specific mandate of the Task Force for Safer Childhood Vaccines. It provides in its entirety as follows:

a. General Rule – In the administration of this subtitle and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall:

(1) promote the development of Childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on the effective date of this part and promote the refinement of such vaccines; and

(2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.

b. Task Force:

(1) The Secretary shall establish a task force on safer childhood vaccines which shall consist of the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Director of the Centers for Disease Control.

(2) The Director of the National Institutes of Health shall serve as chairman of the task force.

(3) In consultation with the Advisory Commission on Childhood Vaccines, the task force shall prepare recommendations to the Secretary concerning implementation of the requirements of subsection (a).

c. Report – Within two years after the effective date of this part, and periodically thereafter, the Secretary shall prepare and transmit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the actions taken pursuant to subsection (a) during the preceding two-year period.

**Box 1. Section 2127(b) of the Public Health Service Act created the Task Force on Safer Childhood Vaccines.**

## VACCINE SAFETY: APPROACH OF THE TASK FORCE

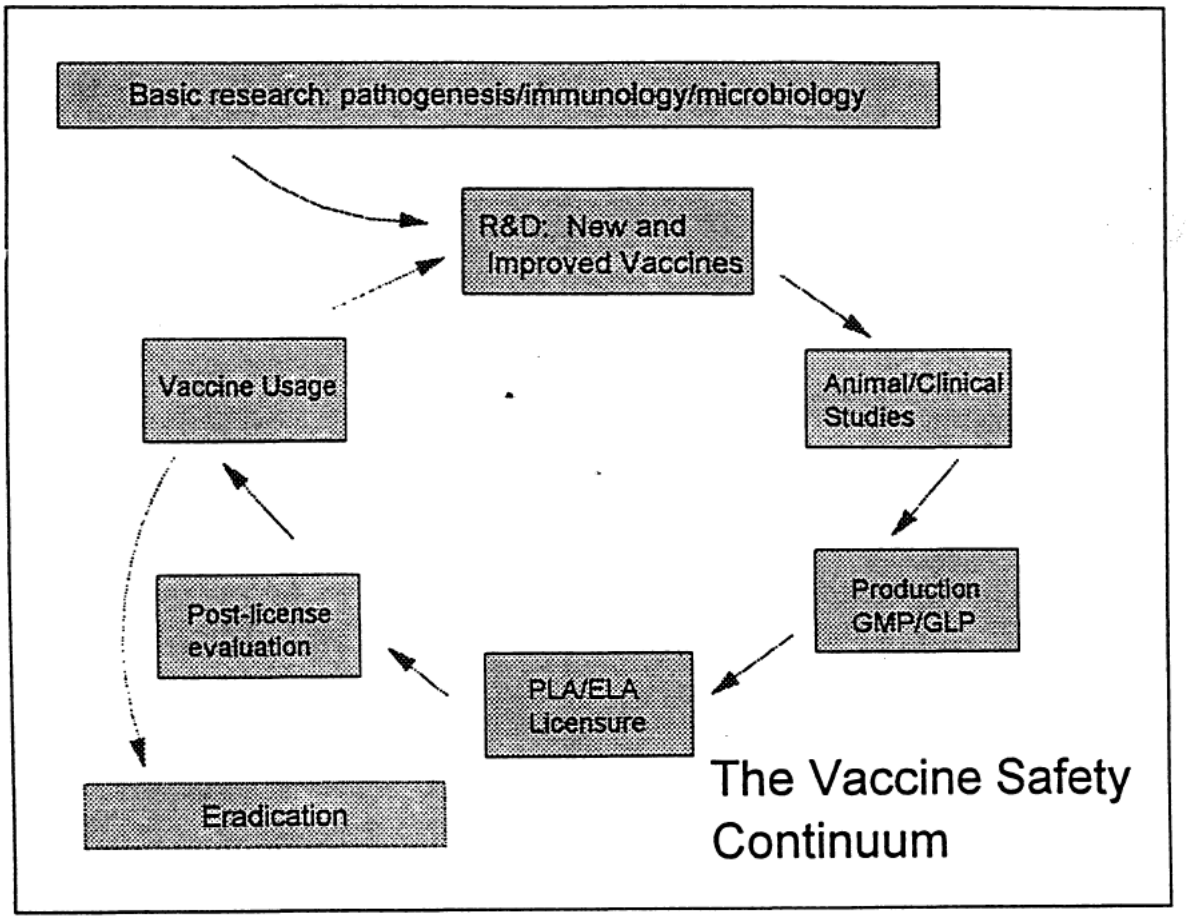
In order to meet its charge and carry out the reporting requirements under the Act, the TFSCV 1) reviewed and summarized safety issues previously identified regarding vaccines currently in use; 2) reviewed existing policies and procedures currently in place to assure the safety of vaccines; and 3) determined options of improving the existing structures in place to assure vaccine safety. As a result of these reviews, the Task Force provides to the Secretary a series of recommendations designed to further enhance vaccine safety.

The Task Force executed this agenda through a series of meetings during which detailed outlines, position papers and other documents were used to facilitate discussion. In considering its broad mandate to review vaccine safety and make recommendations, the Task Force examined alternative approaches. Because two comprehensive, congressionally-mandated reviews of safety issues for the childhood vaccines were underway by the Institute of Medicine, co-funded by NIAID, NVPO/OASH, CDC, and HRSA, the detailed examination of vaccine safety issues for each of the licensed vaccines was considered duplicative and not attempted.

The Task Force elected to examine the systems in place to assure vaccine safety, specifically because of its fundamental premise that the assurance of safety of the vaccine supply is the result of a network of diverse activities that cross-cut agency responsibilities as well as the field of vaccinology (Figure 2: Vaccine Safety Continuum). This "continuum" of activities, from research through development, testing of experimental vaccines, production methodology, and regulation, surveillance for infectious diseases, establishment of routine criteria for the in-vitro and animal

testing of every lot of vaccine released post-licensure (by manufacturers, confirmed by FDA), re-evaluation of efficacy and safety post-licensure, and the safe use of vaccines in clinical practice, are all examples of some of the activities or systems required to assure the safety of a single vial of vaccine. Furthermore, the loci for the "vaccine safety activities" are immensely diverse, and include the laboratories of basic researchers and clinical investigators, research laboratories and production suites of vaccine companies, review by regulatory agencies, as well as the appropriate storage conditions for vaccine in each immunization clinic.

**FIGURE 2. The Vaccine Safety Continuum**




It is essential to recognize that a number of vaccine safety-related activities took place during the deliberations of the Task Force, reflecting a dynamic field driven by both legislated activities and programmatic activities resulting from the rapid development of research technologies and vaccines. Because the field is relatively small, the same small group of PHS personnel participated in these as necessary. Although not a full compilation, Box 2 highlights associated and relevant vaccine-safety activities from 1990-1995.

## Box 2. Selected Vaccine Safety Activities, 1990-1995

- As mandated by Section 312, a study sponsored by the PHS was conducted by the IOM and resulted in publication of the report on the adverse effects of pertussis and rubella vaccines (IOM, 1991).

- As required under Section 313, a second study was undertaken on the adverse effects of the other childhood vaccines (IOM, 1993). Two addenda were requested by the PHS to examine research strategies for vaccine adverse event evaluation, as well as and both were published in 1994 (IOM, 1994).

- An in-depth evaluation of vaccine labels and package inserts, as well as one public meeting, were conducted by the FDA, as required under Section 314 of the Act. This project continues.

- The Vaccine Adverse Events Reporting System (VAERS) was implemented by the FDA and CDC, and a number of presentations on the design and analysis of this system presented in 1994 to the Task Force, as well as to the ACCV, VRBPAC, and NVAC. Progress reports to these groups continue.

- The Large Linked Data Bases (LLDBs) were established by the CDC (see Appendix 7) to focus on the study of vaccine safety, utilization and efficacy post-licensure.

- Publication of Guidelines and Points to Consider documents by FDA on a variety of safety related issues, including such topics as combination vaccines and their evaluation and PTC cell lines used in manufacture of biological products.

- The PHS sponsored scientific workshops which address vaccine safety, such as:

  The Protective and Disease Enhancing-Immune Response to RSV - May 1993 (Anderson and Heilman, 1995)
  Combination Vaccines - July 1993 (Combination Vaccines, 1995)
  Harmonization of Adverse Event Reporting - September 1993
  Meningococcal vaccine candidates - February 1994
  DNA Vaccines - February 1996

- Research initiatives specifically targeted to address issues of vaccine safety: Respiratory syncytial virus (RSV) - Request for applications (RFA) entitled "Mechanism of RSV Vaccine Immunopotentiation" issued by NIAID in FY 1994.

- Recognition and evaluation of vaccine safety problems: Mumps (non-U.S. strain) vaccine and associated encephalitis in other countries.

- Investigations of the risk of Guillain-Barré Syndrome following influenza immunization by the CDC.

## VACCINES: UNIQUE PHARMACEUTICALS

A number of factors serve to differentiate the development, manufacture, and regulation of vaccines from other pharmaceutical products. Since vaccines are given to healthy infants, children, and adults, acceptable risks for these agents must be minimal indeed to assure continued public trust, and therefore maximize acceptance of immunization. Unlike many other pharmaceutical agents, most vaccines are used only a few times in an individual's lifetime, leading to fewer opportunities to examine their impact, as well a much more restricted market. In addition, many vaccines are mandated by the states, and are frequently required for school, day care, or employment entry. No other drugs or biologic agents have such widespread mandated use. Vaccination is an integral part of public health practice and well-baby care.

All of these factors have led to the evolution of an infrastructure for the delivery of immunization services that focuses primarily on the delivery of vaccines to infants and children. Immunization practices have been developed with the aims of making vaccines safe and effective for the child and convenient for the parent.

In many countries, immunization programs and policies are constantly under review and revision. In the United States, immunization policies are reviewed by established committees which seek representation from parents, professional societies, state government and federal agencies. Thus, changes in vaccination schedules, such as the addition of newly licensed vaccines into the standard of care, require broad consensus and are relatively slower and more complex than changes in other classes of agents within the pharmaceutical industry. This process has become increasingly complex with the need to co-administer newly licensed vaccines, often produced by different manufacturers, and assure their safety and efficacy.

Finally, new vaccines are extensively studied for safety and are unlikely to proceed through lengthy development steps to licensure if there is evidence of severe adverse reactions. After licensure, pediatric vaccines are given to very large numbers of infants at a time when neurologic and other medical conditions are developing, implies that some clinical syndromes, however rare and for whatever cause, may occur in temporal association with vaccination. This makes the assessment of safety and of attributable risk problematic for both new and old vaccines. These and other factors have helped to shape the special nature of the vaccine industry at a time of unparalleled growth in the basic sciences and in the technologies for vaccine development.

### Public Health and Individual Perspectives on Immunization

In universal immunization programs, where vaccines are aimed at the entire healthy pediatric population, there is an inherent conflict between the interests of the individual and of the community (Fine and Clarkson 1986, Nokes and Anderson, 1991). The tension between individual risks and public benefits is the classic ethical dilemma for public health. For the individual, the goal of immunization is protection from disease. Informed adults are able to judge the benefits derived from this protection with the risks associated with the vaccine. Similarly, when parents assess the value of immunization for their healthy child they must make a decision in the context of the risks associated with immunization. For some vaccines - such as the use of rabies vaccine after exposure to a potentially rabid animal- the risks and benefits are clear and evident. For other vaccines, the risks and benefits are not as obvious. This is especially true if the vaccine to be given protects against a disease which has become rare due to vaccination, or a disease which is not perceived as a significant threat.

In contrast, the public health interest places emphasis on reducing disease in the community. High rates of immunization may be required to achieve this goal, and for some diseases where there is

person-to-person transmission, reducing the incidence by vaccination results in "herd immunity", with the potential risk reduced for all community members regardless of their individual immunization status. While a disease is prevalent and feared, the benefits of immunization for the individual far outweighs the risk of disease, both in the minds of public and of the medical community. The early years of polio immunization exemplify this situation. But if a vaccine is effective, and high coverage levels for vaccination are sustained over time, the disease, such as polio, will become rare. In this context, the risks of immunizations may be seen as outweighing the benefits from the perspective of one individual - but that is only true as long as everyone else other than that individual remains immunized and the risk of transmission of poliovirus remains low. All documented cases of polio acquired in the U.S. since 1980 have been caused by the live oral polio vaccine; while the numbers have been very small (4 to 9 cases per year) they represent a risk that may increasingly outweigh the value of oral immunization for some parents and physicians. The change in the risk-to-benefit ratio is heightened in the face of an alternative means of prevention, in this case, enhanced Inactivated Polio Vaccine (eIPV). This topic, and the selection of the optimal polio immunization policy in the face of elimination of polio from the Americas, will be discussed at a series of meetings hosted by the NVP, IOM and ACIP, beginning in summer 1995.

Herd immunity may be maintained only if the majority of parents accept immunizations for their children. When overall population coverage falls, the pool of susceptible persons increases in size. This situation was demonstrated by the 1989-1990 measles epidemic. While coverage rates for measles vaccine across the country were accepatable by age 5, high risk populations remained unprotected from measles until school age. The population of susceptible children was sufficient to permit sustained transmission of measles virus, with the largest outbreak of measles since 1977. In 1990 alone, 27,672 cases of measles were reported in the U.S. Tragically, the largest annual number of measles deaths (89) since 1971 resulted from this epidemic (MMWR, 1991).

When communities require vaccination for entry into school, day care, or other public settings, some parents may feel they are being coerced, especially if there are concerns that the procedure is potentially dangerous or unnecessary. Such was the situation in Sweden when public concerns over both the efficacy and safety of their "whole cell" pertussis vaccine led to cessation of routine pertussis immunization in 1979 (Gershon, 1990). As a result, pertussis again became an epidemic disease of childhood. A similar situation occurred in Japan, where two deaths after pertussis immunizations led to widespread refusal of the vaccine. The number of cases in Japan then rose from less than 1,000 cases per year in 1975 to 13,105 in 1979, with a case fatality rate of about one percent (Gershon, 1990). In the mid-1980's, the American public's perception of the risks associated with the whole cell pertussis vaccine caused concern for the viability of the immunization program in the United States. In 1985, two manufacturers ceased production of DTP vaccine due to litigation concerns or manufacturing difficulties, leaving a single U.S. manufacturer of the vaccine to supply the needs of the U.S. The price of DTP vaccine increased 5-fold in that year and threatened national immunization efforts by making vaccine unaffordable to many programs.

## THE DYNAMIC NATURE OF THE VACCINE FIELD

Advances in basic research fields such as immunology, microbiology and genetics, together with advances in applied technology, have opened windows of opportunity for the development of new vaccines and the improvement of older ones. These advances have also generated new challenges in vaccine safety, as novel classes of immunogens are investigated and new technologies applied. At the same time, new emerging pathogens, such as the Human Immunodeficiency Virus (HIV), Borrelia budgdorferi (the cause of Lyme disease), and strains of M. tuberculosis resistant to current antimicrobial agents present opportunities for vaccine development. In addition, there is a consensus that the development of safe and effective vaccines may be crucial for control of many

"older" infectious diseases. Examples of such conditions include malaria and gonorrhea, both of which continue to be serious public health problems despite the existence of effective treatment.

Changes in health care organization and improvements in computer technology now permit computerized vaccinationa and medical records to be linked on large numbers of individuals. Compared to passive surveillance systems, such Large-Linked Data Bases (LLDBs) permit a more accurate assessment of whether rare serious vaccine reactions occur, and if so, at what rate and whether any risk factors might be identified. The development of regional or even national computerized vaccine registries may one day improve the recording and accessibility of the actual vaccines and combinations received by an individual, as well as ensure recording of his/her contraindications to future doses.

**The impact of basic research and technologic advances on vaccine safety.**

The Task Force reviewed examples of research and technologic advances in the fields of microbiology, immunology, and chemistry, which may have important implications for vaccine safety in the future. For example, the detailed molecular analysis of attenuation of live vaccine strains may permit the design of vaccines which are unlikely to revert to virulence. A number of new antigen production systems, employing recombinant technologies and chemical conjugation technologies, have already resulted in totally new vaccines of known purity or enhanced efficacy. The need for easily delivered combination vaccines is fostered by novel technologies for their creation. However, the use of new technologies for the production and delivery of antigens will generate additional challenges to vaccine safety. Some vaccines produced with these technologies are currently at the basic research stage, while others have been tested in humans. As technologies are develop, safety must remain a priority concern. Finally, the enhancement of the specific immune response to vaccine candidates by immunologic adjuvants is often necessary for the new approaches utilizing highly purified antigens. The development and testing of any immunoenhancer is driven and limited by concerns about its safety in humans.

A summary of this review, and examples of applications of these new technologies, is presented as Appendix 3.

**New and emergent infectious diseases: unexpected challenges to vaccinology**

In the last decade several new or previously unidentified infectious diseases have been recognized as important pathogens, and are currently the subject of intensive vaccine research. A brief summary of the development of vaccines for three emergent pathogens, HIV, MDR-Tuberculosis, and Lyme Disease, is presented in Appendix 4.

**Vaccine Safety Issues - Past and current**

Vaccine safety has a long history. Some of the currently recommended childhood vaccines have been in use for decades and have intensively scrutinized safety profiles and well described adverse events associated with their use. Others are new agents, with which we have relatively only a few years of clinical experience. A number of vaccines used in the past are no longer licensed in the U.S. because of safety concerns, and the memory of these discontinued agents and the problems associated with them appropriately persists. Appendix 1 lists the childhood vaccines, examples of the safety issues associated with their use, and the responses that have been made to address those issues. The most recent reviews by the Institute of Medicine (1991, 1993), summarized in Appendix 8, reviewed many conditions for a possible causal relation to vaccines and concluded that most of the conditions in question were "cagetory 2" - that is, the data were insufficient to evaluate.

### The Laboratory Evaluation of Vaccine Safety - New technologies

New technologies pose challenges and offer novel approaches to the in-vitro evaluation of safety. The rapid evolution of technologies has dramatically changed the ways in which vaccine safety can be assessed. The new classes of vaccines, including conjugates, recombinants, combinations and vectored vaccines, will require the use of these novel biotechnologies and evaluation mechanisms. Older vaccines, developed about 40 years ago, are being reevaluated using these approaches. Combination vaccines in particular will present a major challenge to laboratory evaluations. The current situation is rapidly changing and presents powerful new tools for the evaluation of vaccine safety. A description of these technologies and their potential application to vaccine safety is presented in Appendix 5.

### The Clinical Evaluation of Vaccine Safety - New technologies

The tools for the clinical evaluation of vaccine safety have developed over the past 50 years, and include clinical trial methodology, biostatistics, and epidemiology, as well as more recent application of molecular epidemiology (Chen, 1994b). Thus, it was possible to utilize viral culture techniques to confirm the hypothesis of polio-vaccine-associated poliomyelitis which was based on epidemiologic data. The successful application of molecular epidemiology to enhance surveillance and subsequent vaccine development has been demonstrated in influenza as well as measles.

### Evolving Recommendations for Use of Vaccines

As additional information emerges, adjustments and revisions are made to recommendations for the use of vaccines. Examples of new types of data that have caused a change in immunization practice are changes in epidemiology of the disease and improvements in vaccines that alter target groups for immunization. The Advisory Committee on Immunization Practices (ACIP) of the CDC monitors the epidemiology of the target diseases and use of vaccines, and makes recommendation to the Public Health Service on immunization strategies that will result in the assurance of public health. Other groups, such as the "Redbook Committee" of the American Academy of Pediatrics, as well as the American College of Physicians and the American Association of Family Physicians, contribute to the evolution of use recommendations, as well as to their implementation. The effective dissemination of new immunization recommendations is an important factor in a successful immunization program, especially for the introduction of a new vaccine, and may require approaches that will reach all target audiences: pediatricians, family practitioners, nurses, patients and parents, as well as policy makers.

Appendix 6 describes examples of immunization recommendations which have evolved over time. These examples demonstrate that assessment of safety and efficacy are closely linked; that immunization practices must promote both in order to protect the public health; and that assuring both requires an ongoing evaluation of the efficacy of immunization practices, as well as their safety. The examples pertain to three diseases and their respective vaccines, namely, measles, pertussis and hepatitis B.

## THE EXISTING CAPABILITY TO ASSESS VACCINE SAFETY - Vaccine Evaluation and Licensure

### Existing structures

The FDA is the agency responsible for assuring that only vaccines that have been demonstrated to be safe and effective are licensed and sold in the United States. The authority to regulate vaccines and other biologics is based in both the Public Health Service Act (PHSA) and the Food, Drug and

Cosmetic Act. As a result of this legislation, a variety of safeguards are in place to insure and maintain the safety of vaccines. The CDC also plays a major role in developing appropriate recommendations for vaccine use, under advise from the Advisory Committee on Immunization Practices (ACIP), as well as conducting post-marketing surveillance on vaccine safety and efficacy. Prior to describing this framework and its implications for assessing safety, it is useful to recall that the definition of safety formally used by the FDA is stated in the biologics regulation as the *relative freedom from harmful effect*, and safety cannot be absolutely guaranteed.

The procedures and processes that are in place evolve as new knowledge is gained. As defined by the relevant Code of Federal Regulations, these procedures include extensive laboratory testing of experimental materials before any use in human subjects, the use of ethics review committees to evaluate and monitor such experimental use, the extensive evaluation in animal model systems, and the rigorous requirements to report and investigate any adverse events associated with the use of a vaccine.

**Components**

Laboratory and animal studies The assessment of a vaccine's safety begins long before any testing in humans. A candidate vaccine must first be tested extensively in animals and in the laboratory. The primary objective of this phase of the testing is to ascertain if the candidate vaccine exhibits any reactogenicity or toxicity. Usually these studies are also used to gain insight into the product's immunologic properties. Laboratory assays and/or animal models have been developed for many infectious diseases and they have proven to be extremely useful in characterizing the product prior to their experimental use in human subjects. Often modifications in vaccines introduced at this stage of development are selected to improve immunogenicity and reduce reactogenicity.

Studies in human subjects In general, clinical studies of all pharmaceutical products proceed along a logical path that involves three discrete phases (See Box 3). During vaccine development, all three phases are carefully monitored by the FDA using the Investigational New Drug Application (INDA or, more commonly - IND).

**BOX 3. Three phases of vaccine clinical trials**

- Phase I trials involve very small numbers of healthy subjects (20-80). These studies are used to determine whether the product has any gross toxicity problems and to acquire safety and immunogenicity data on dose-related immune responses.
- Phase 2 trials utilize controls and larger numbers of subjects (100-200). They are designed to further assess product safety, as well as obtain preliminary information on dosing and efficacy.
- Phase 3 trials use large numbers of subjects (several hundred to thousands) to confirm safety and effectiveness, define risk-benefit relationships, gather information to be incorporated into the package insert, and support marketing approval. This phase may also be used to collect data concerning lot consistency and the acceptability of manufacturing scale-up operations.

Review of protocol by committees and regulatory authorities. After the product has been evaluated in animals, the sponsor of the candidate vaccine may apply for permission to conduct testing in humans. Before testing begins, an application must be submitted to FDA which, among other

things, will certify that a properly constituted Institutional Review Board (IRB) has reviewed and approved the proposed study and has found that all appropriate safeguards for human subject protection are in place, including signed informed consent. A summary of the preclinical testing is also submitted. If the clinical study proposed is the first evaluation of a vaccine candidate in humans, it is quite common practice to restrict the number of subjects to be studied. Additional studies are permitted only after this first study is completed and there is a confirmation of the general safety of the candidate vaccine. The test protocol is described in detail and contains the study design and a plan for the statistical analysis. Information on the product's composition, assays of purity and potency, and method of manufacture are included. Furthermore, the investigators must provide a statement of their qualifications and experience. If, after reviewing the above information, FDA determines that the test subjects will not be exposed to any untoward risk, the clinical trials may proceed. To assure continued safeguards, the investigators are required, during the course of the trials, to submit annual reports and notify FDA of any adverse events.

The IND system of phased clinical trials has several advantages for safety assessment. First of all, the phased entry of subjects allows only small numbers of people to be exposed to unknown risk; more individuals are exposed as more safety data are collected. Should serious reactions occur, the trial can be suspended until the problem is resolved. The system also allows for the characterization of adverse events in terms of dose relationships, age relationships, and drug interactions. Finally, all phases of testing are rigorously monitored by the FDA.

Licensure application After completion of the trials, if the data indicate that the product is safe and effective, the manufacturer may submit an application to FDA to market the product. For a biological product, such as a vaccine, two license applications are required:

- The first, a product license application (PLA), includes a description of the manufacturing process, the results of the clinical trials which demonstrate the product to be safe and effective, results of required testing on consistency lots of product, product specifications and a copy of the package insert which will accompany the product.

- The second, an establishment license application (ELA), contains information about the facility used to make the product and contains data demonstrating that the facility is in compliance with the requirements of 21 CFR 600 and 211. These regulations cover the facility's personnel, quality control, buildings, equipment, containers, records, and distribution procedures to assure a consistent, safe product.

Using an internal panel of scientific experts, the FDA reviews and evaluates the data submitted in these applications, resolves any manufacturing deficiencies, conducts its own testing of the consistency lots, permits its own analysis of the clinical and laboratory data submitted, consults with outside panels of experts as appropriate (the VRBPAC), reviews the labeling (including the sections containing the precautions, warnings and contraindications), revises the labeling as needed, and obtains commitments from the manufacturer for certain post-approval safety-related actions. In addition, a pre-licensing inspection of the production facility is performed to verify the data submitted in the establishment and product license applications. When FDA is assured that the data are complete and adequate and demonstrate that the product is safe and effective, the establishment and product licenses are issued and the manufacturer may begin to distribute the product.

Assessment of Vaccine Safety Post-licensure The primary assessment of vaccine safety occurs during investigative clinical trials. Information from these trials serves as the basis for the initial package insert and label statements. However, phase 4 clinical trials involve a relatively limited

number of subjects and study duration and thus will probably only detect the more common adverse acute adverse reaction. These trials are also conducted among a healthier and more homogenous population than that which ultimately uses the vaccine. Information about rare, delayed or population-specific adverse reactions can only be gathered after vaccine licensure when the vaccine is used more widely. Post-licensure monitoring of the product safety continues at several levels.

*1) Lot release tests* - Each lot of product is routinely tested by the manufacturer, usually for general safety, potency, sterility, purity, and identity. Currently, the manufacturer tests each lot of vaccine with a battery of assays appropriate for each specific vaccine as described in 21 CFR (Parts 600-639) as well as other considerations often addressed in the relevant Points To Consider document. Test results and samples from each lot are sent to FDA by the manufacturer. FDA reviews the test results and performs confirmatory testing on the samples as needed. If the data are satisfactory, the manufacturer is authorized to distribute the lot.

*2) Facility Inspections* - All facilities used in the manufacture of vaccines are inspected at least biannually. During these inspections, experts in Good Manufacturing Practices (GMP) and vaccine research from the FDA headquarters and regional offices carefully examine and evaluate for compliance with FDA's regulations the physical plant, its production records, behaviors of plant personnel, adverse event reports and any other documents or matters which may indicate the quality of operations at that site.

Should any violations of regulations be observed, they are recorded in a formal memo (called an FD483 by FDA) and at the end of the inspection each is discussed with the management as to the cause of the infraction, the remedial action to be taken and how each will be prevented from reoccuring. The U.S. is blessed with a vaccine industry that has a long history of producing safe and effective vaccines while operating in this highly monitored environment, and so while violations are occassionally observed, most are of a very minor nature (e.g. failure to place initals on the production log for each and every step of the manufacturing process) and are not an immediate safety concern. However, should an issue of imminent safety hazard be discovered, the FDA can halt production and distribution almost immediately. In addition, FDA in such a circumstance can request a recall which is a return of all suspected products to the manufacturer.

*3) Approval for changes* - Another mechanism FDA uses to maintain control over product safety after licensure is the requirement that all changes in indication or usage for the product, labeling, production methods, key personnel, testing or quality assurance be submitted prior to implementation to FDA for approval. Upon receipt of the submission, a thorough evalution for each change is made and FDA may require additional testing or validation to occur to satisfy safety concerns before approval is granted.

Examples of major actions in which FDA has participated to assure product safety are listed in Box 4.

## Box 4: FDA Reports of Vaccine Safety Problems Recognized through FDA review and testing procedures

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|---|---|
| 1971 | The diphtheria component of a lot of DTP failed its detoxification test. The vaccine lot was recalled. No injuries reported. |
| 1974 | A lot of DTP was recalled because of a failure to resuspend after mixture (flocculent present). No injuries reported. |
| 1980 | Through reporting, the manufacturer detected that its DTP vaccine was producing sterile abscesses. The FDA was prepared to halt further release of the vaccine, but no action was necessary because the manufacturer voluntary withdrew the vaccine from the market. |
| 1989 | Equine influenza vaccine was inadvertently placed in vials labeled DTP. The "DTP" vaccine lot was recalled. No vials containing mislabeled vaccine were believed to have left the manufacturer's facilities. No injuries reported. |
| 1992 | An FDA investigation of a key clinical study being conducted to support the licensure of acellular pertussis showed that the primary investigator failed to obtain proper consent, maintain adequate records, or appropriately monitor the study. Under FDA directive, the problems were corrected and the investigator was required to sign a consent agreement. The FDA maintained strict surveillance over the investigator and the vaccine licensure process was not undermined. |
| 1992 | A manufacturer made manufacturing and facilities changes without submitting a supplement to its product licenses. An FDA inspection of the new, unlicensed facility was conducted. Before any action could be taken, the company voluntarily withdrew its license to manufacture vaccines. There were no imminent safety problems. |

Assessment of vaccine safety continues after licensure through a variety of activities including a passive reporting system (VAERS), active surveillance in controlled studies, phase 4 studies, lot release tests and facility inspections. FDA has published proposed rules for reporting of adverse events for drugs and biologicals in order to provide uniformity and facilitate reporting (Federal Register, October 27, 1994). The proposed rules also cover amendments to clinical study design and requirements for IND safety reporting.

**Background - Reporting systems** Both active and passive surveillance methods are used to monitor product safety post-licensure (phase 4 trials). These studies are extremely valuable since a rare reaction (i.e., one that occurs only once in thousands of doses) may not be detected in even large clinical trials performed before licensure. Both are needed, however, for early detection if a potential vaccine safety problem occurs. This is a responsibility traditionally shared be the CDC and FDA. Historically, the CDC focused primarily on the public sector and safety concerns relevant to the ACIP recommendations - serving as the point of contact for health departments and the public - while the FDA focused on the private sector, manufacturers and regulatory issues. Examples of investigations of vaccine safety conducted by he CDC are listed in Box 4b.

**Box 4b. Examples of Vaccine Safety Studies Conducted/Funded by CDC**

1. Associations between poliomyelitis and inactivated (Langmuir) and oral polio vaccine (Schoberger, Strebel)
2. A cluster of infants with SIDS following DTP vaccination (Bernier, Griffin, Chen)
3. Possible association of GBS and influenza vaccine (Schonberger, Safranaek, Chen)
4. A cluster of abscesses following DTP vaccination (Stetler, Simor)
5. Risk of neurologic illness following DTP (SONIC, Walker, Griffin) or MMR vaccine (Walker, Griffin)
6. Risk of invasive bacterial disease after DTP vaccine (Griffin).

*4)* *Passive reporting systems* Historically, passive reporting has been the major (and in most countries, the only) post licensure surveillance conducted for vaccine adverse events. The main goals of such systems are to detect any new, previously unreported reaction, or any changes in rates of known reactions. Because of their national scope, they are requently the only means available to monitor extremely rare adverse events. Passive reporting systems, such as VAERS, act primarily as signal generating systems. Trends and clusters can be detected through continuous statistical monitoring of the database. However, passive surveillance systems are limited by the possibility of underreporting, reporting bias and the difficulty in calculating incidence rates, even if full reporting were to take place. as hypotheses to be tested within more rigerous, prospectively designed systems.

Examples of vaccine-related safety hazards that have been detected in the past by passive surveillance systems are the inadequate inactivation of poliomyelitis vaccine (The Cutter Incident) and the severe reactions to rabies vaccine produced in human diploid cells. CDC and FDA implemented in 1990 a passive reporting system for monitoring those adverse events associated with vaccination. This system is known as VAERS (Vaccine Adverse Events Reporting System). Like most passive reporting systems, under-reporting of events occurs (Rosenthal, 1995). Nevertheless, the system has been demonstrated to be useful in identifying new vaccine reactions, such as alopecia after hepatitis B vaccine, and changes in known vaccine related adverse events. After five million doses of DTaP were distributed for use as fourth and fifth doses, rates of adverse events reported to VAERS after DTaP are about one third that of DTP, confirming their greater safety found in prelicensure clinical trials.

> The VAERS program is a merger of the CDC Monitoring System for Adverse Events Following Immunization (MSAEFI) and the vaccine reports contained in the FDA Spontaneous Reporting System (SRS) programs and was implemented on November 1, 1990. VAERS provides a central foci for reporting of specific adverse events associated with vaccines listed in the Vaccine Injury Table required by Section 2125 of the Public Health Service Act, as well as any other vaccine adverse events occurring after licensed vaccines in the U.S. Its pre-addressed, postage-paid forms are widely distributed via annual mailout to physicians likely to administer vaccines.
>
> Between January 1, 1991 and December 31, 1994, the VAERS program received over 45,000 reports. About 40% of reports come from manufacturers, 24% from private health care providers, and 35% from State Health Departments. Approximately 17% of all reports concern serious events, resulting in life-threatening illness, hospitalization, permanent

disability or death. Regulations requiring that vaccine manufacturers report all known adverse events to the FDA were published in 1994 (Federal Register). Should a threat to safety be identified, FDA has the authority to recall any product from the marketplace.

The greatest shortcoming of passive surveillance system is the general inability to draw conclusions on causal association. They general lack unique laboratories for the evaluation fo clinical syndromes that permit conclusions on causility to be drawn. They also represent a limited segment of the information necessary for the epidemiologic assessment of vaccine causality.

*5)* *Active surveillance studies* Active surveillance studies can be controlled, targeted and prospective. They can be used to detect rare, serious events not detected in the limited pre-licensure clinical trials or to validate the signal of a potential adverse event detected by passive reporting. Compared to passive reports, they offer the advantage of a rigerous scientific design, and allow meaningful conclusions to be drawn from the data. For rare adverse events, which may lack unique laboratory or clinical features, these studies are the only scientific approach answer the questions of causality. However, such studies are often large, long-term and costly. For these reasons, relatively few such studies have been done for the purpose of vaccine safety. In recent years, FDA has obtained commitments from manufacturers to continue surveillance on the use of new products to gain additional safety data.

One attractive approach to active surveillance is the use of Large-Linked Database Systems (LLDBs), in which computer linkages join immunization data to outpatient and inpatient records in large HMOs or other patient databases. This approach may provide appropriate control groups and facilitate analysis by speeding data collection. The CDC explored the use of such LLDBs for smaller studies beginning in the mid-1980's. In 1990, CDC contracted with four HMO's with a total population which represents 2% of the US, for active surveillance studies of vaccine safety (Appendix 7). Preliminary results from this study indicate that this project will help fill many of the gaps and limitations in knowledge of vaccine safety found by the IOM.

Very rare outcomes, such as GBS, may still be too rare to be studies using LLDBs. Ad hoc epidemiologic studies are designed and conducted, as was done for GBS following the 1990-91 and 1993-94 influenza seasons.

6) *Other Phase 4 studies*. Concurrent with license approval, FDA may seek a manufacturer's agreement to conduct certain postmarketing studies (Phase 4) to obtain additional information on the product's risks, benefits and optimal use. These studies include, but are not limited to studies assessing schedule of administration, use with other products and adverse event associations. Phase 4 studies conducted by the manufacturer are reportable to the FDA for review. Such studies numbering tens of thousands of persons are still unable to address questions about rare reactions.

7) Continued research Active research programs are the foundation for ongoing vaccine safety assessment. As new products and new processes are developed, basic research programs on immunologic mechanisms must be in place to assess potential safety issues. In the event of an alleged cluster of adverse events, it is essential that investigators, support services, and resources are readily available to conduct a timely product evaluation and epidemiological study. Public concern over vaccine-associated deaths presents a difficult challenge to public health officials and epidemiologists, and clearly requires significant attention.

**Existing advisory bodies which review vaccine safety issues.**

Vaccine safety oversight resides among a broad group of advisory committees and governmental groups. Most notable are the DHHS Immunization-related advisory committees including: the Advisory Commission on Childhood Vaccines (ACCV), the Immunization Practices Advisory Committee (ACIP), the Microbiology and Infectious Diseases Review Advisory Committee (MIDRAC) of the NIAID, the National Vaccine Advisory Committee (NVAC), and the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The Department of Defense is advised on vaccine and other issues by the Armed Forces Epidemiological Board (AFEB).

Overall coordination of programs involving both broad vaccine issues and vaccine safety falls within the purview of the National Vaccine Program's Inter-Agency Group (IAG). Whereas safety is not the main or only focus of these groups, aspects of vaccine safety coordination and oversight exist within all of them.

The ACCV advises the Secretary of DHHS on the National Vaccine Injury Compensation Program, which provides compensation for certain vaccine-related injuries or deaths and recommends research related to vaccine injuries. This body advises the Secretary regarding the need for childhood vaccine products that result in fewer significant adverse reactions.

The ACIP provides advice to the Secretary, the Assistant Secretary for Health, and the Director, Centers for Disease Control and Prevention, in their responsibilities to assist States and localities in the prevention and control of communicable diseases. Additionally, the Committee reviews and reports on immunization practices and recommends improvements in the national immunization effort. Most recently, Congress added the selection of vaccines for the Vaccines for Children program to the ACIP mandate.

The MIDRAC provides the scientific review of contract proposals and grant applications in microbiology and infectious diseases for the National Institute of Allergy and Infectious Diseases. In this capacity they advise on policy, planning, and operational matters related to research and development and evaluation of programs and projects in these fields.

The NVAC advises the Secretary, Health and Human Services, and the National Vaccine Program on a broad spectrum of issues relating to vaccine development, licensure, testing, distribution, and use. Several aspects directly involving safety issues include: recommending research priorities and other measures to be taken to enhance the safety and efficacy of vaccines, monitoring research and developmental activities with regard to new or improved vaccines, and coordinating public and professional information/education activities including those associated with adverse events and contraindications.

The VRBPAC reviews and evaluates for the Food and Drug Administration (FDA) data relating to the safety, effectiveness, and appropriate use of vaccines and related biological products requiring licensure by the FDA, which are intended for use in the prevention, treatment, or diagnosis of human diseases. The committee also considers the quality and relevance of FDA's research program.

The Department of Defense's advisory body, the Armed Forces Epidemiological Board (AFEB) has responsibilities to advise the Assistant Secretary of Defense and the Surgeons General of the military departments on operational programs, policy development and research programs and requirements for the prevention of disease and injury and promotion of health. The Subcommittee on Disease Control is tasked to provide the latest scientific evaluations and recommendations

concerning immunizations, chemoprophylaxis and therapy, as well as disease surveillance, prevention and control.

Overall Federal responsibility for implementation of the National Vaccine Program (NVP) and coordination of Federal immunization activities falls to the InterAgency Group (IAG), created in the early 1980's. The need for such interagency cooperation in solving national vaccine problems was first defined during the Swine Flu epidemic, with the formation of an influenza work group. Early efforts to coordinate federal vaccine responsibilities led to the formation of an Interagency Group to Monitor Vaccine Development, Production and Usage in 1980. Upon the formation of the NVP, this group was chaired by the NVP. Representatives from each of the vaccine agencies (Agency for International Development, Centers for Disease Control and Prevention, Department of Defense, Food and Drug Administration, and the National Institutes of Health) make recommendations about vaccine policy and operational issues. Specific responsibilities related to vaccine safety oversight involve the monitoring of research and developmental activities with regard to new or improved vaccines, and coordinating public and professional information/education activities involving vaccine recommendations, adverse events and contraindications.

The Committee on Infectious Diseases of the American Academy of Pediatrics formulates and revises guidelines for the prevention and control of infectious diseases in children, published in the "Red Book" (AAP, 1994). These represent consensus developed by the Committee in conjunction with liaison representatives (from the Centers for Disease Control and Prevention, the Food and Drug Administration, the National Institutes of Health, the Canadian Paediatric Society, the National Vaccine Program, as well as the ACIP and others) based on review of the published literature as well as presentations of additional data from experts.

It is inevitable that overlap of vaccine safety responsibilities occurs among these various committees and groups. One such area of perceived overlap is in the area of vaccine use recommendations. The ACIP advises the Centers for Disease Control in development of use recommendations for vaccines. The Red Book Committee provides use recommendations to the pediatricians. The VRBPAC makes use recommendations that are reflected in licensure decisions and labeling of vaccine products. These various recommendations have at times been inconsistent, creating confusion for the agencies and health care providers.

The need for harmonization of use recommendations within the U.S. has intensified. The recent licensure of the acellular pertussis vaccine for the fourth and fifth doses highlighted the need to assure closer coordination of vaccine licensure with the development of vaccine use recommendations and the availability of an adequate supply of the newly available vaccine. There currently exists an informal practice to coordinate impending actions on new and improved vaccines. For example, a CDC/ACIP representative attends VRBPAC meetings, and FDA is represented at ACIP meetings. Further measures to assure coordination of impending actions on new and improved vaccines have been discussed and recently reviewed (Halsey et al, 1995).

Determination of the need for further vaccine safety research also falls to several committees and groups. The MIDRAC evaluates the NIAID research agenda from the broadest perspective, ACCV advises the Secretary regarding the need for safer childhood vaccines, and the NVAC monitors research activities related to new or improved vaccines. The IAG identifies gaps in research involving vaccine safety. Where possible, the vaccine agencies address these gaps or devise strategies to do so.

## The Complexity of Assessing Safety of Vaccines

The development of sensitive and specific methods to assess the safety of existing and new vaccines has proven to be a challenge. Although relatively small-scale, Phase II-IV studies have been useful in estimating the incidence of minor, common adverse reactions (e.g., local erythema, fever, etc.), the medical community and consumers are most concerned about severe, life-threatening events. While such events are believed to occur at a frequency of $<1$ per million doses administered, universal application of these vaccines, particularly during childhood, dictates both the need and obligation to develop better means for detection. In spite of this well recognized need, however, practical barriers exist and will continue to be a challenge, as illustrated by the following examples:

OPV and reversion to neurovirulence Paralysis following administration of oral poliovirus vaccine (OPV) is believed to occur at a frequency of $\sim 1$ case per 2.5 million doses distributed, and has constituted the sole form of paralytic poliomyelitis acquired in the U.S. for the past 15 years. Rapid advances in molecular biology have provided opportunities to learn more about which gene segments of the Sabin strains may be associated with reversion to neurovirulence. Scientists and public health officials are currently evaluating a molecular biologic assay to replace the current test for neurovirulence. The exclusive use of enhanced-potency, inactivated vaccine could theoretically eliminate vaccine-associated paralysis, and public health officials are currently considering the potential for changing the currently successful policy, which relies on the nearly exclusive use of OPV.

Difficulty of conducting safety evaluations Nearly all childhood vaccines are administered on multiple occasions during the first year of life, a time when rare neurological, immunological, and other disorders may manifest. Vaccination is nearly a universally accepted and recommended practice, so that controlled evaluations to compare the incidence of such events in vaccinated vs. unvaccinated children have become increasingly difficult to conduct. Although large-scale studies involving thousands or millions of children could theoretically provide large enough comparisons groups based on differences in the timing of vaccination in relation to these extremely rare clinical disorders, the lack of definitive case definitions for some of these events, combined with difficulties in controlling for a myriad of confounding variables, have also made these studies virtually impossible to carry out. The cost of such studies has also been considered prohibitive, particularly in the environment of efforts to reduce spiralling health care costs.

TABLE 1,

| Rate of condition in the vaccinated | Rate of condition in the controls | Total sample size required (1:1 control and vaccinated) |
|---|---|---|
| 1/100 | 0.5/100 | 9,348 |
| 1/1,000 | 0.5/1,000 | 94,000 |
| 1/10,000 | 0.5/10,000 | 942,071 |
| 1/100,000 | 0.5/100,000 | 9,421,372 |

Table 1 illustrates the sample sizes required to answer a question of association or causality for a rare adverse event that occurs in children, with the following assumptions: the condition is assumed to be severe and easily recognized, and the condition may be caused by vaccines as well as other stimuli. If we were to conduct a clinical trial to detect a difference of twice the rate between vaccinated and unvaccinated (power $=.80$ and $\alpha=0.025$), then the sample size needed for a simple, randomized clinical trial to demonstrate the difference between vaccinated and unvaccinated when the condition occurred in 1/100,000 vaccinated would be approximately would be 9.5 million subjects.

The rare and serious adverse events we are most concerned about are believed to occur less frequently than 1/1,000 children. And the assumptions of an ideal clinical trial are rarely met in real life, especially in the setting of post-licensure surveillance: conditions are not fully diagnosed or similarly expressed in every child, they may not always develop within days or hours of immunization, and children are not randomly assigned to vaccination or non-vaccination. For these reasons, other study designs, such as case control studies, are also used to study very rare outcomes.

Combination vaccines Vaccine innovation has been successful when directed towards the development of products which include a number of antigens. The most recent example are the combined DTP-Hib vaccines. Although simultaneous administration of multiple antigens in a combination vaccine reduces the number of injections and simplifies the immunization schedule, the incidence of common and serious adverse events associated with each antigen becomes extremely difficult to estimate. This problem will become even more evident within the next few years, when combination products containing DTaP, Hib, hepatitis B, and inactivated poliovirus are likely to become available. Yet, these products are required so that each of the individual vaccines is successfully administered to those at risk.

Conjugate vaccines The pre-licensure data available for an entirely new product, such as the Hib conjugate vaccines, is based on studies in hundreds or thousands, but not hundreds of thousands of children. The existence of an elevated risk for very rare adverse events cannot be ruled out solely with experience in a clinical trial population and prior to experience in the population at large. the evaluation of safety for a new vaccine administered in infancy can also be complicated further with the co-administration of a vaccine with other childhood vaccines that may themselves be reactogenic. The clinical evaluation of co-administered vaccines made by two different manufacturers, such as HBV and DTP, may require support and the availability of testing sites acceptable to both manufacturers.

## GAPS - EXISTING CAPABILITY TO ASSESS VACCINE SAFETY

The reviews published by the IOM (1991, 1993) summarized in Appendix 8, reviewed 76 medical conditions or the scientific data available to assess possible causal relation to vaccines. The IOM found that for about 2/3 of these conditions, there was either no evidence bearing on the association, or the evidnece was insufficient to accept or reject a causal relation. Both IOM studies identified major haps and limitations in current knowledge on vaccine safety, and made suggestions on research needs.

On the basis of the preceding review, the Task Force noted that a number of areas could be strengthened in order to assure the Nation's capability to assess vaccine safety. As required by Congress, these were recognized as gaps and defined specific needs that could be addressed within the context of the Task Force recommendations. The needs were of three types; the first, related to vaccine information; the second, related to safe practices for using vaccines, and the third related to the need for scientific and technological improvements. Many of the gaps noted in the IOM report, as well as by the review of the Task Force, were due to intrinsic methodologic difficulties in condicting vaccine safety evaluations. Others are in the process of being addressed by activities undertaken over the past four years. Substantial resources and commitment will be needed to fully address the identified shortcomings.

Vaccine Information Needs

- Assess the effectiveness of the vaccine package inserts.
- Assess and improve health provider knowledge and patient awareness of immunization risks and benefits.
- Develop, or where possible improve, educational standards on immunization within curricula of health care professionals.
- Design Vaccine Information Materials which clearly and effectively communicate instructions on use, precautions and contraindications so that the vaccines will be administered in the safest and most effective manner (these are already available as "second generation" documents after exhaustive review and revision by the CDC).
- Improve communication with families and persons affected by vaccine adverse events.
- Develop programs to enhance the reporting and accuracy of reports of potential adverse events by health care providers in both the public and private health sectors.

Safe Use of Vaccines - Needs

- Assure availability of data on complex schedules, including studies of simultaneous administration and combination vaccines, in order to assure the development of safe recommendations and immunization practices.
- Ensure consistency and harmonization of use recommendations among advisory groups in the U.S.

Improve Surveillance - Needs

- Develop standardized analyses of VAERS data, with particular emphasis on the evaluation of data for new vaccines, and on co-administration of vaccines.
- Enhance analyses of serious events, and specifically deaths, reported to VAERS, by exploring its use as a registry of potential rare serious adverse events.
- Incorporate adverse event recording into developing state or regional immunization tracking systems, in order to permit the rapid and detailed evaluation of adverse events.

Intrinsic Improvements in the Vaccines

- Apply emerging technologies to development of improved tests for evaluation of safety, as well as new laboratory standards.
- Conduct review of scientific advances in the field of vaccine adverse event methodology (note reviews published by IOM in 1994).
- Conduct phase IV studies to continue to monitor and assess vaccine safety, efficacy and effectiveness, including LLDBs and other approaches.

## EXISTING CAPABILITY TO PROMOTE DEVELOPMENT, MAKE AND ASSURE IMPROVEMENTS

### Existing capabilities

Several branches of the U.S. Public Health Service have responsibilities and capabilities in the field of vaccine research and development. The FDA has regulatory and research roles of key importance. Its Center for Biologics Evaluation and Research (CBER) has played a pivotal role in vaccine research for many years. The NIH, and its member institutes, support research, both basic and clinical, that will lead to the improvement of the Nation's health, as their principal mandate.

The CDC, and its National Center for Infectious Diseases and National Immunization Program, are also actively involved.

**The contribution of basic and clinical research**

The National Institutes of Health (NIH) play a major role in basic and clinical research on vaccine improvement and development within the PHS. A number of institutes within the NIH support vaccine research, including the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), and the National Institute of Child Health and Human Development (NICHD). Nationally, other research institutions, vaccine companies, the FDA, CDC and DoD, and biotechnology firms also conduct or support basic, developmental and clinical research on vaccines. The participating federal agencies also play a central role in research interactions with vaccine companies, international agencies, private organizations and academic institutions. In 1981, NIAID founded its Program for the Accelerated Development of Vaccines to focus and enhance research activities leading to new vaccines for important diseases, and to improve existing vaccines, especially as regards safety. Since the Program's inception, eleven new or improved vaccines have become available, and three have been added to the recommended childhood immunization schedule. In 1990, NIH expanded its role as the lead Public Health Service agency for vaccine research with the intensification of efforts to evaluate acellular pertussis vaccines. NIH works closely with the other agencies of the PHS involved in the Nation's research efforts to improve vaccines and prevent disease.

Defining Pathogenesis of Disease To develop effective vaccines it is essential to understand the pathogenic mechanisms by which infectious organisms cause disease in humans. An example is basic research on microbial virulence factors such as the capsular antigens of *S. aureus*, polysaccharides that have been identified as key components in the disease mechanisms of this important bacterial pathogen.

Expected Immunologic Response to Natural Disease The generation of effective vaccines requires the understanding of human immune responses to disease-causing agents. Vaccines seek to replicate the protective immune responses of natural diseases without producing symptoms or pathology. For new generations of vaccines, especially for those diseases against which we rely on mucosal immunity, basic research on these immune responses is a priority. An NIH-funded research group began preclinical testing in 1991, focusing on the systematic exploration of microencapsulation of tetanus toxoid, influenza, and recombinant rotavirus vaccines. NIH also sponsors research on mucosal immunity aimed at creating vaccines for sexually transmitted diseases, and on the enteric mucosal response that will be critically important to the development of oral vaccines.

Determining Serologic Correlates of Immunity The evaluation of the immunogenicity of new vaccines hinges on our ability to identify protective immune responses. These serologic correlates of immunity remain unclear for a number of targeted diseases and are a research priority. NIAID is currently sponsoring an intensive investigation into the serologic correlates of immunity against *B. pertussis* as part of the acellular pertussis vaccine initiative.

Identify Candidate Immunogens The evolution of basic sciences and biotechnology has allowed for new classes of vaccines made up of immunogenic proteins and polysaccharides of infectious agents. The first of these to be licensed, the *H. influenzae* type b conjugate vaccines, have demonstrated the safety and practicality of this approach. Investigators are currently attempting to identify candidate immunogens of a number of organisms, including Group B streptococci (GBS) and HIV.

Intramural Capability In addition to supporting research through the awarding of grants and contracts, NIH supports intramural research laboratories which focus on vaccine development and play an important role in the improvement of vaccine safety. The glycoconjugate technology which allowed for the development of the *H. influenzae* conjugate vaccines was the product of intramural research at NICHD. Intramural scientists have active programs in a number of disease/vaccine areas, including respiratory syncytial virus, rotavirus, malaria and dengue. Other agencies, such as FDA and DoD (Department of Defense) and CDC, also support internal laboratory research.

Workshops to enhance communication and peer review The workshop mechanism allows the PHS to convene focused scientific meetings on issues relating to vaccine improvement and development. When a number of new acellular vaccines against pertussis were under development, NIH convened a workshop involving principal investigators and sponsors of each of these vaccines to discuss safety issues of these acellular agents. These gatherings are an opportunity for researchers to meet, share results, and have their work informally reviewed by peers.

Extramural Process and Peer Review There are a number of mechanisms through which NIH stimulates and supports research on vaccine improvement and development. In addition to the intramural capability and workshops mechanisms, NIH operates extensive extramural programs including the award of research grants, training grants, and extramural research contracts.

NIH extramural research grants largely support investigator-initiated research. However, both solicited and unsolicited proposals are awarded funding through this mechanism. These grants provide critical supports to basic research in immunology, microbiology, and pathogenesis that are essential to the eventual development of safe and effective vaccines. All extramural grant proposals are peer reviewed by extra-divisional expert panels, a process that helps to assure the highest standards of science.

Training grants are an important part of NIH's support of basic research. This mechanism helps ensure the manpower resources necessary for the nation's vaccine research agenda. These grants typically support junior researchers for three to five years. Training grants are also used to sustain and develop research infrastructure and capacity in institutions outside the PHS. Training grants, like research grants, are peer reviewed.

The research contracts mechanism functions as a procurement process for targeted research. These contracts are typically initiated by the institutes to fulfill specific unmet research needs. An example is the group of contracts awarded for the development of the animal model systems needed for vaccine research. Other contracts are used to answer specific questions regarding the safety of candidate vaccines in humans. These contracts, because they involve research protocols of candidate vaccines with human subjects, are closely coordinated with the FDA and vaccine companies.

The vaccine industry, comprised of the major vaccine manufacturers as well as biotechnology companies, sponsors or conducts a significant amount of vaccine research. However, because their results are not always published, and because their financial records are confidential, the extent of this committment can only be estimated. Clearly, they contribute significantly to the development and licensure of new vaccines.

Standards for Human Testing A number of standards have been developed to guide the testing of any medical intervention in humans. In the U.S., conduct of Federally-supported or FDA-regulated clinical studies is regulated via legislation that includes, among other safeguards, Institutional Review Boards (IRB) and informed consent. In the U.S., the IRB must have at least five members, and may be institutional or independent. The IRB must review and approve an investigator's

protocol and informed consent form before a study may be initiated. In addition, the IRB reviews periodic reports from the investigator, as well as reports after any serious adverse reactions or changes in the clinical trial, investigates any aspects of the clinical trial to ensure patients safety, terminates the trial if appropriate, and maintains appropriate records of all correspondence regarding the clinical trial.

Phase I-2 Clinical Trials: Immunogenicity and Safety The three phases of clinical vaccine research in humans have been previously described (see Box 3). NIAID established the Vaccine and Treatment Evaluation Units (VTEUs) in the 1960's with the capability to do phase I and 2 vaccine trials. Currently, NIAID supports seven non-AIDS VTEUs at university-based medical research institutions around the country to accelerate the testing of new and improved vaccines in early human trials for safety, immunogenicity, and protective efficacy. Their experience with vaccine trials, combined with their access to population groups for relevant studies, makes the VTEUs a national resource for the early evaluation of vaccines. A number of other clinical centers conduct Phase I and 2 trials directly sponsored by industry.

Phase 3 Clinical Trials: Efficacy and Safety Phase 3 clinical trials are safety and efficacy evaluations usually done with large numbers of subjects drawn from the population at risk. The PHS has sponsored a number of Phase 3 trials of improved or new vaccines, such as the NIH-sponsored acellular pertussis trials currently underway in Sweden and Italy. Most often, these are sponsored directly by industry.

Communication with the vaccine research community Communication and coordination among a number of related agencies are essential for an effective immunization and vaccine research and development program. NIH, individual research groups, the Inter-Agency Group of the NVPO, vaccine companies, international organizations, and government agencies in other countries are important participants in this process. The NIH-sponsored acellular pertussis trial underway in Italy demonstrates effectiveness and need for communication. The Italian trial is a coordinated effort involving NIH, the Italian Ministry of Health, the Italian Public Health Service, and four private vaccine manufacturers. In addition, the FDA has had considerable input into the protocol for the study, the CDC was involved in epidemiologic training of the staff, WHO held an important meeting to discuss the pertussis clinical case definition that would be used in this and other trials, and a number of universities and medical centers in the U.S. were involved in the phase I and II trials in which the vaccines for the Italian trial were evaluated and selected. Communication and coordination of this order help ensure that research is based on a true consensus within the world vaccine community, and that whatever results such a large and expensive trial generates will be of high order and validity.

**The contributions of manufacturers**

Vaccine companies in the United States, in addition to manufacturing the final product, conduct a significant amount of research and vaccine development, the vast majority of the national expertise in process development in pilot lot production of vaccines, and conduct or support clinical studies leading to licensure. In the U.S. they are an integral part of the vaccine research and immunization system. The federal agencies, be they regulatory, immunization program or research-based, work with the vaccine companies to achieve development and safety goals.

Improvements in vaccine safety are enhanced by the regulatory framework used by FDA to assure vaccine safety and efficacy. Field-developed current Good Manufacturing Practices (cGMP) standards ensure that manufacturers use the best available technology for vaccine production. The word "current", in FDA's interpretation, means that without having to amend the regulations FDA expects that manufacturers will use state-of-the-art technology and procedures. FDA has

demonstrated capability, if a health hazard is imminent, to recall from the market any questionable vaccine and not allow it to be marketed until the problem is resolved (see Box 4). In addition, FDA has the ability to require that a manufacturer revise the warnings, precautions, and/or contraindications in its product literature if a new type of adverse reaction is detected.

**The contribution of surveillance, vaccine recommendations and epidemiologic studies.**

Epidemiology of disease and risk factors Understanding the epidemiology and the risk factors for any disease is important to its control and prevention, and thus is a priority for the Centers for Disease Control and Prevention (CDC). This is especially true for a vaccine-preventable disease in order to 1) monitor the impact of vaccines on reduction of their target diseases (e.g. *Hib*), and 2) monitor any changes in disease epidemiology that may require changes in vaccine recommendations (e.g. two dose measles vaccination schedule). Such information on disease incidence and risk is critical to overall risk-benefit analysis and recommendations for vaccine use to the public.

Provision of vaccine to the public sector As the nation's largest single purchaser and provider of vaccines, and because vaccines are critical to its duties in disease prevention, CDC has maintained a major interest in vaccine safety since its founding. A separate Vaccine Safety Activity was created at CDC in 1990 to provide a focus for this important area. Vaccinations provide not only substantial benefit to the individual but also indirectly benefit non-immune individuals. It is therefore important to ensure all persons have access to certain vaccinations. Historically the public sector, through immunization grants administered by CDC, has been estimated to provide approximately half of the childhood vaccines for each birth cohort. This may increase under the Vaccines for Children Program. For special vaccination programs like the National Influenza Program of 1976, the public sector may provide almost all the vaccine.

Risk/benefit assessment The ACIP is an advisory group comprised of independent experts on immunization and public health. The ACIP meets three times annually to weigh the risks and benefits of different vaccinations and arrive at recommendations for the use of such vaccines for the American public. Accurate and timely information on vaccine safety is critical to the ACIP in its deliberations and recommendations.

Warnings/Use Instructions The need has developed for concise and accurate summary of the risks and benefits of individual vaccines, understandable to the general public. CDC first developed such one page Important Information Sheets (IIS) for use by all administrators of publicly purchased vaccines in the 1970s. These IIS were updated periodically and aimed at a 5th grade reading level. These IIS also provided instructions to vaccinees on how to report adverse events. In 1988, the development of the Vaccine Information Pamphlets (VIP) mandated by the PHS Act was undertaken by CDC. More simplified sets of Vaccine Information Materials (VIMs) were developed, pre-tested and released in 1994. VIMs for the childhood vaccines are now available.

Distribution/Storage/Stockpile In order to assure the Nation's supply of needed vaccines, CDC negotiates contracts annually with vaccine manufacturers which include the manufacturer agreement to store and distribute the vaccine directly to eligible vaccine administrators. Because of the small number of vaccine manufacturers and to minimize the risk of vaccine shortages, a system of rotating stockpile of vaccine for the public sector has been established. Safety is served in two ways: the continued supply to the immunization program, and the required standards (dating, storage, etc.) for maintaining the stockpile.

Field surveillance/Adverse reaction reporting CDC implemented adverse events surveillance in conjunction with the 1976 National Influenza Immunization Program. Subsequently, the MSAEFI system was established for the public sector in 1978. Major improvements in MSAEFI were

implemented in 1985. Following the passage of NCVIA, CDC has worked closely with FDA to develop and implement VAERS, a merger of the CDC MSAEFI and FDA SRS databases. CDC serves as the contracting office for VAERS.

Special ad hoc epidemiologic studies Due to expertise in conducting disease surveillance and epidemiologic studies, and its close contact with local health departments who may first hear of potential vaccine safety concerns, the CDC has conducted or funded a number of epidemiologic studies to assess potential vaccine safety problems through the years. Examples of such ad hoc studies are listed in Box 4a. Of note are the creation of the LLDB since 1990 to permit more timely assessment of potential signals generated by VAERS and other sources for vaccine causation. CDC has also developed several new methodologies to improve PHS' ability to examine vaccine safety issues, e.g. safety profiles, linkage of MSAEFI reports with pre-vaccine release lab tests. Other sources of such studies include the NIH (NIH sponsored epidemiologic study of SIDS and DTP vaccine (Hoffman)) and the UK Medical Research Council (National Childhood Encephalopathy Study).

Monitor vaccine use In order to monitor the national immunization program, a number of types of data on the use of vaccines are compiled by CDC for use as indicators of program effectiveness. Such data provide important sources of information on vaccine coverage, but also provide the data to estimate denominators for VAERS reports from the public sector, to derive approximate rates for vaccine adverse events. Such information includes doses purchased and distributed via the public sector contract, doses administered by age and antigen data, and estimated vaccine coverage via a variety of surveys (e.g. National Health Information Survey, retrospective school-entry surveys). FDA maintains confidential data on numbers of doses in each vaccine lot distributed for use in the U.S.

In the future, vaccination registries may provide accurate and timely data for use in vaccine safety studies.

Interaction with global immunization programs (EPI and GPV). The PHS agencies participate in and contribute to the global immunization, research and regulatory programs, both by consultations and collaborations with individual countries, as well as participation in multilateral projects. For example, the CDC provides substantial technical assistance to various national immunization programs and the WHO Expanded Program on Immunizations (EPI). In vaccine safety, CDC staff has assisted WHO and the Pan American Health Organization to develop draft guidelines on vaccine adverse event surveillance. Because an infrastructure for disease surveillance has been developed via the national EPI's, it has been possible to build vaccine adverse event surveillance onto an existing framework. CDC staff has also consulted closely with other national EPI's as ad hoc vaccine safety concerns arose (e.g. mumps vaccine aseptic meningitis, allergies to Japanese encephalitis vaccine, cluster of deaths following DTP vaccine). Similarly, FDA is participating in the plans and discussions of international harmonization of adverse event reporting systems so that eventually a database of all safety experience with vaccines can be easily consulted. NIH has supported trials in high risk endemic areas, and provides scientific expertise and collaborates with the newly formed Global Program on Vaccines and Immunization (GPVI).

## EXPERIENCES LEADING TO THE DEVELOPMENT OF IMPROVED VACCINES

### Reports/concerns of adverse events which led to the development of new vaccines

During the past several decades, reports from a number of widely divergent sources ultimately served as the principal driving force behind the development of alternative preparations for existing

vaccines. Previously cited examples include the development of acellular pertussis vaccines. Several other examples follow:

Measles - killed/live Although both live-attenuated and inactivated measles virus vaccines were licensed in 1963, many providers preferred the inactivated preparation because of the reduced incidence of acute side effects. Within a few years, however, it became apparent that prior receipt of the inactivated vaccine was associated with a relatively severe, "atypical" clinical syndrome when recipients were exposed to natural measles virus infection. Once this problem was recognized, inactivated measles vaccines was no longer recommended. Attention was directed towards the development of live vaccines that were further attenuated. Inactivated measles vaccines have not been used since that time, and "atypical" measles is no longer reported.

Rubella The early rubella vaccines, first licensed in 1969, including some produced in dog kidney cells that were associated with a relatively high incidence of arthralgia. The occurrence of these and other systemic reactions (e.g., fever) prompted the development of alternative products grown in duck embryo, and later, in human diploid cells. This field was recently reviewed, and emphasis was placed on the development of an animal model for arthritis cause by rubella (Frey, 1994).

Influenza Although inactivated influenza vaccines have been widely used for a number of decades, severe adverse reactions other than anaphylaxis were not described until 1976. At that time, the development and mass application of the so-called "swine" influenza vaccine led to an increasing number of reports of Guillain-Barré syndrome within the 30-day period following vaccination. Subsequent investigation confirmed the association of this influenza vaccine with GBS. However, large-scale studies of GBS during the subsequent 3-year period showed no association with influenza antigens other than the swine-like strain.

Hepatitis B The development and licensure of plasma-derived hepatitis B vaccine was heralded as an important event in the prevention of hepatitis B and hepatocellular carcinoma. Unfortunately, plasma donors for vaccine production were often populations at high risk for HIV/AIDS, causing concern about the potential for HIV transmission through vaccination, even though HIV, if present in the plasma, would have been destroyed in the manufacturing process. Nevertheless, the perception of a risk probably reduced hepatits B immunization rates. An effective, genetically engineered vaccine produced in yeast was subsequently licensed in the U.S. As a consequence of this, the plasma-derived product is no longer available in the U.S. Although considered to be safe and effective, the plasma-derived product is only used in certain developing countries.

Rabies Prior to 1988, the use of preexposure booster doses of human diploid cell rabies vaccine (HDCV) was limited because ~6% of recipients who received both primary and booster vaccinations with HDCV developed serum sickness-like reactions. These reactions were believed to be due to the presence of a small amount of human serum albumin that was rendered allergenic by the beta-propiolactone used in making HDCV. To counteract this problem, the Michigan Department of Public Health developed an absorbed rabies vaccine (licensed in 1988) that did not use human serum albumin as a component in the cell culture medium; consequently, albumin is not present when beta-propiolactone is added to inactivate the virus.

**Significant modifications of manufacturing processes**

Over the years, FDA has become aware of circumstances which cast doubts on the safety of specific vaccines. FDA and its predecessor, the Division of Biological Standards (DBS) in these situations concentrated their efforts to quickly arrive at solutions to the problems. One example occurred when the work of Sweet and Hilleman indicated that simian virus 40 (SV40) was commonly present in tissue cultures prepared from rhesus monkey kidney cells. This newly

recognized agent produced no cytopathologenic changes, which made it very difficult to detect by the safety testing in place at the time.

The publication in March, 1961 that SV40 was relatively resistant to the formalin used to inactivate viruses during manufacture caused great concern. DBS scientists investigated vaccines which were produced in these cultures and discovered several lots containing infectious SV40. Although the virus produced no discernible disease, other DBS personnel demonstrated that volunteers inoculated with a massive dose of the virus developed antibodies and sometimes shed virus in their nasopharyngeal secretions. DBS felt that this evidence, while not extremely alarming, called for action. Taking advantage of the observation that while the virus causes no change in rhesus cell it regularly did so in the cytoplasm of tissue culture cells prepared from the African green monkey kidney, DBS on May 5, 1961 required that safety testing in green monkey kidney cells be included as part of the battery of regulatory assays. Quick action on DBS's part minimized the number of Americans who might have been exposed to this agent (Meyer, 1962).

## GAPS IN CAPABILITY TO PROMOTE DEVELOPMENT AND ASSURE IMPROVEMENTS IN VACCINE SAFETY

Based on this review, the Task Force recognized the following gaps in the U.S. capability to promote development and assure improvements in vaccine safety.

Promoting development and vaccine improvements - GENERAL NEEDS

1. Conduct a detailed review of Section 312 and Section 313 congressionally-mandated reports conducted and published by the IOM, and assure appropriate response by PHS Results are summarized in Appendix 8. (In progress)
2. Understand host factors associated with adverse events to vaccines.
3. Identify microbial properties and mechanisms for adverse events.
4. Determine factors associated with the use of vaccines (licensed as well as IND) in the face of national emergencies (Pandemic Influenza Preparedness, in progress).

## TASK FORCE ON SAFER CHILDHOOD VACCINES
## RECOMMENDATIONS

Although a number of vaccine-preventable diseases, such as poliomyelitis, may be controlled and even eliminated globally, others, such as pertussis, tetanus or diphtheria, are not candidates for eradication. Therefore, vaccination against these diseases must be continued to protect each new cohort of infants, both in the United States and globally. For this reason, it is anticipated that the potential for perceived risks due to reports of adverse events will also continue indefinitely, and the systems required to assure vaccine safety must be maintained. In fact, given the development of new technologies for the development, production, manufacture, regulation and administration of vaccines reviewed, the vaccine safety network for the United States must be enhanced in order to evaluate the new candidates appropriately. In order to ensure the continued public acceptance of vaccines, close monitoring of potential adverse events and adverse reactions, adequate scientific evaluation of hypothesized associations, and appropriate responses to newly identified risks of vaccines, including research and targeted development of new technologies and vaccines, are critical.

In order to address gaps and assure the continuing safety of vaccines, the Task Force developed the following recommendations:

1. ***Assess and address national concerns about the risks and benefits of vaccines to enhance the education of the public, families, and health care professionals.*** To do this, the PHS should:

   A) Identify public and health care professionals' concerns, attitudes and knowledge regarding immunization and the benefits and risks of vaccination.

   B) Develop appropriate interventions to enhance knowledge about vaccines, their benefits and risks, reporting of adverse events, immunization programs and their public health impact.

2. **Strengthen the national capability to conduct research and development needed to promote the licensure of safer vaccines.**

   A) Where an association is demonstrated between an adverse event and vaccination, ensure that these findings will lead to relevant research and vaccine improvements.

      i) Ensure appropriate initiation of regulatory review and action.

      ii) Conduct studies of the biologic basis for vaccine adverse events.

      iii) Develop, where feasible, epidemiologic and biologic markers or tests that would be useful to evaluate, predict and/or determine risk groups for adverse events.

      iv) Use, wherever possible, vaccines that have been modified or improved to avoid adverse events.

   B) Important areas for consideration are new assays to detect potential mediators of adverse events, laboratory correlates of vaccine safety and efficacy, and evaluation of the safety of novel methods to enhance immunogenicity, vaccine delivery technologies, and to improve the thermostability of vaccines.

C) Foster the active participation of industry, and increase public-private collaborations, in development of safer vaccines of public health priority.

D) Encourage research and development leading to production of "limited-use vaccines" of potential public health importance through public support of R&D and strengthened interactions with industry. The development of vaccines for limited populations poses special challenges to the development of a safety profile.

3. **Strengthen the national capability to conduct surveillance of vaccine preventable diseases, and to evaluate potential adverse events and vaccine efficacy.**

A) Integrate government post-licensure surveillance activities to enhance the evaluation of available information, identify gaps and reduce the duplication of efforts, with emphasis on the following areas:

i) Develop new methods and approaches for the post-licensure evaluation of the safety and efficacy of vaccines and vaccine uses, and assure that the appropriate studies are conducted.

a) Prospectively evaluate vaccine safety and efficacy in large populations, including adults, to help identify the association of vaccination with serious but uncommon adverse events. Develop methodology for investigating causality of rare events in vaccine recipients, especially in a highly immunized population.

b) Develop novel methods and approaches for the detection and evaluation of adverse events associated with new vaccines or new uses of vaccines in order to supplement systems such as VAERS. Identify and incorporate other U.S. and international agencies/survey systems that collect information relevant to the evaluation of adverse events.

ii) Identify any differences in rates of adverse events associated with the simultaneous and/or combined administration of vaccines.

B) Ensure the adequacy of clinical data to support new recommendations for vaccine use, and when appropriate, conduct studies to address safety considerations.

C) Improve the coordination and sharing of data concerning standards, adverse event reports, and analyses with other national control and epidemiologic authorities, including the World Health Organization (*Regulatory Harmonization*). The U.S. should participate in the development of an international network to monitor vaccine safety, taking advantage of both the differences and similarities in the vaccines used and the national health care structure.

D) Encourage the participation of industry in the collection and analysis of data to address both pre- and post-licensure vaccine safety.

1) Review industry's responsibilities and existing role in collection, receipt, follow-up and analysis of received adverse event reports.

2) In consultation with vaccine manufacturers, develop procedures to optimize the collection of complete data and the analysis of reports (1) by product category, (2) by analysis of product-specific data (by company), and (3) by analysis of product interaction with other vaccines (in combination).

4. **The Task Force recommends that the Interagency Vaccine Group, comprised of representatives from those agencies involved in vaccine research, development, evaluation, regulation and immunization activities, be charged with the ongoing responsibility to assure that appropriate vaccine safety activities are carried out.** In accordance with the original mandate to integrate the Nation's vaccine efforts, the NVPO could serve as the Secretariat for this group, and would provide a locus for assuring action towards emergent vaccine safety needs.

A) The IAVG would monitor the vaccine safety activities of the various agencies and work to improve interagency communication. It would also facilitate and monitor progress on the investigation and evaluation of reports of serious and/or frequent adverse events.

i) Evaluate data relevant to vaccine safety which may be currently scattered among various agencies and manufacturers.

ii) Assure periodic reviews of the safety of licensed vaccines, and of their recommended immunization schedules. If appropriate, propose studies to address areas where additional data may be informative or supportive, such as in special target groups or programs.

iii) Assure effective communication with existing advisory committees that focus on vaccines and immunization, including specifically the ACCV, ACIP, NVAC and VRBPAC.

B) The IAVG would be expected to seek routine technical consultation from an expert external advisory body.

## APPENDIX 1. EXAMPLES OF VACCINE SAFETY ISSUES RECOMMENDED CHILDHOOD VACCINES

| Vaccine | Safety Issue | Evidence and risk groups | Status |
|---|---|---|---|
| OPV | Vaccine Associated Paralytic Polio | 4-8 cases/year in the US, or less than 1/ 1 million doses. Risk is higher after first dose of OPV (1/500,000) than for subsequent doses (1/2,000,000) (Streble, 1992) More significant in immunocompromised. Mechanism is purported to be reversion of live attenuated vaccine strain to neurovirulence. | ➢ Basic research ongoing to define and detect determinants of neurovirulence (FDA, NIH).<br><br>➢ OPV not to be used in immunocompromised patients and in infants/children who are household contacts of persons with altered immunity.<br><br>➢ Discussion regarding sequential eIPV/OPV schedules to decrease risk of VAP (ACIP, AAP). |
| | Adventitious Agents--SV40 | SV40 (Simian Virus 40), a viral contaminant of OPV vaccine grown in monkey kidney cell culture was found to be carcinogenic in hamsters (Eddy, 1961). | ➢ Surveillance of population showed no increased incidence of cancer due to SV40 (Mortimer, 1981).<br><br>➢ New technologies developed (PCR) to detect adventitious agents.<br><br>➢ New cell culture production systems developed (OPV grown in VERO lines) to obviate need for primary monkey cells. |
| IPV | Incomplete Inactivation | Cutter incident (1955) - 204 vaccine-related cases of polio due to improper production (Nathanson, 1963). Recent history is of excellent safety profile (IOM, 1993). | ➢ Strict control over manufacturing standards, consistency, purity, and inactivation. Current regulations include additional filtration systems. |
| | Anaphylaxis | Neomycin and streptomycin used in manufacture to prevent bacterial contamination. Local reactions in allergic individuals. Theoretical risk. | ➢ Surveillance is ongoing. |

| Vaccine | Safety Issue | Evidence and risk groups | Status |
|---|---|---|---|
| DTP | Protracted, inconsolable crying | Causal relation ascribed to cellular pertussis component. Rate is estimated at 0.1 to 6% of vaccinated infants. (IOM, 1991). Typically resolves in under 24 hours. | ➢ Seven large scale acellular pertussis (DTaP) clinical trials in Sweden, Italy, Germany, Senegal (three sponsored by NIH). |
| | Acute encephalopathy | IOM found evidence consistent with a causal relation. Studies contradictory: meta-analysis suggests that risk is between 0.0 to 10.5 cases per million doses. (IOM, 1991) | ➢ Acellular pertussis vaccine trials underway.<br>➢ Evaluation of VAERS system for reporting for adverse neurologic events.<br>➢ Comparison of efficiency of reporting between VAERS and LLDBs for febrile seizures ongoing (Chen, p.c.) |
| | Shock and "unusual shock-like state" -- hypotonicity, hyporesponsive episodes (HHE) | IOM found evidence consistent with a causal relation. Evidence contradictory and rates vary from 3.5 to 291 cases per 100,000 injections. | ➢ Comparisons of DTP and DTaP in pending clinical trials may help resolve the role of cellular pertussis components in these reactions. |
| | Sudden infant death syndrome (SIDS) | All studies reviewed by the IOM have suggested either no relationship between SIDS and DTP immunization, or a decrease in SIDS risk for DTP recipients. | ➢ SIDS surveillance and VAERS surveillance continue. |
| | Anaphylaxis | Causation is not ascribed to any one component. Rate is estimated at 2/100,000 doses (IOM, 1991). | ➢ Basic research in immunopathology. |

| Vaccine | Safety Issue | Evidence and risk groups | Status |
|---|---|---|---|
| MMR | Acute Arthropathy and Arthritis | IOM found evidence consistent with a causal relation attributed to rubella component. Rate 13-15 % of adult women, much lower among men, children, and infants. | ➢ Epidemiologic studies underway<br>➢ Large Linked Data Bases may help clarify this issue |
| | Chronic arthritis | IOM found evidence consistent with a causal relation attributed to Rubella component. Not enough data to determine a rate. | ➢ Epidemiologic studies to evaluate risks and risk factors are being considered. |
| | Anaphylaxis | Has occurred with MMR. The vaccine contains both trace neomycin and trace egg antigens, which are known allergens and immunogens. | ➢ MMR vaccine is contraindicated by a history of allergy or anaphylaxis due to neomycin. Egg allergy is a relative contraindication. Recent studies of safe administration (James, 1995). |
| | Aseptic meningitis | Urabe vaccine mumps strain only: not used in US | ➢ Vaccine removed from European and other markets. Strain not available in U.S. |
| | Subacute Sclerosing Panencephalitis (SSPE) | Rare, severe complication of measles and possibly of measles vaccine strain. SSPE incidence rates have fallen since the widespread use of MMR. Rates estimated at 0.7/million doses of vaccine versus 8.5/million cases of measles.(Johnson & Griffin et al. 1984). 1993 IOM study concluded category 2 - not enough data. | ➢ Passive surveillance for SSPE is ongoing. |
| Hib Conj. | Unknown; few serious AEs described. | Safety profile for very rare reactions (less than 1/100,000 doses) not yet established. | ➢ Recent IOM study includes evaluation of safety issues of this vaccine. PHS review of that study planned. |
| | Anaphylaxis | Has been reported in both US and Finland (1/100,00 doses in the Finnish HibTiter trial.) Not enough data to determine rate. | ➢ Post-licensure surveillance with FDA. |

| Vaccine | Safety Issue | Evidence and risk groups | Status |
|---|---|---|---|
| HBV | Unknown; few serious adverse reactions described. | | ➢ Recent IOM study includes evaluation of safety issues of this vaccine. |
| | Anaphylaxis | Possible reaction. | ➢ 1993 IOM report |
| Comb. vaccine | Potential for change in efficacy or safety profile in some combination vaccines | Altered immunogenicity has been demonstrated with live attenuated vaccines (MMR-VZV as per manufacturer, ACIP).<br><br>DTP-HIB and respiratory diseases. | ➢ Development of safe, effective combinations continues<br><br>➢ Evaluated by FDA Advisory Committee prior to licensure. |
| Td | Anaphylaxis | Local reactions are known to occur. Allergic reactions have been reported, data suggests serious allergic reactions to Td are rare. Anaphylaxis rate in 1985 and 1986 was 6.4 cases/million doses. (Mortimer & Plotkin, 1988) | ➢ Vaccine is contraindicated in patients with a history of allergic reaction.<br><br>➢ Surveillance for adverse events is ongoing. |

APPENDIX 2

## NATIONAL VACCINE LEGISLATION

The Department of Health and Human Services (DHHS) is responsible for a variety of activities related to vaccines. These include supporting, conducting and promoting research on vaccines; regulating the manufacture and distribution of vaccines; promoting and administering vaccination services; and monitoring impact of immunization programs on disease rates. Most of these activities have been part of the Department's mission for decades, while some have been assigned since the enactment of the National Childhood Vaccine Injury Act of 1986 (Public Law 99-660).

The issue of safety is and has been inherent in the Department's administration of its various authorities related to vaccines. Indeed, safety is one of the statutory requirements for licensure of vaccines, whether under the authority of section 351 of the Public Health Service Act, or under the other authorities of the Food and Drug Administration. These include the Food, Drug and Cosmetic Act, expanded by the Durham-Humphrey Amendments of 1951, the Kefauver-Harris Amendments of 1962 and the Drug Regulation Reform Act of 1979. Nevertheless, Public Law 99-660 gave an additional emphasis to this issue in the context of childhood vaccines.

On March 13, 1985 the House Energy and Commerce Committee convened an oversight hearing on biotechnology and its role in vaccine development. The Congress recognized that vaccines and immunization were critical to public health. Also, they concluded that progress in research was providing important opportunities to develop new vaccines against many infectious diseases. The previous decade of disease prevention through immunization had been labeled a global revolution in public health. However, vaccines and immunization were troubled by the liability crisis and perceived disarticulation of the vaccine efforts. In 1986, in response to concerns from parent's groups, vaccine companies, and the medical and public health communities, Congress established the National Vaccine Program (NVP) and the National Childhood Injury Compensation Program (NVICP) under Public Law 99-660.

The NVICP is a no-fault system to compensate children and their families presumed to have suffered serious adverse reactions to mandated vaccines. By establishing this program, Congress aimed also to reduce the threat of tort liability for vaccine manufacturers and thereby stabilize vaccine supply, and to improve the climate for new vaccine research and development. The program is funded through an excise tax imposed on each dose of vaccine sold in the U.S. and by an appropriation from general funds to cover injuries that had occurred prior to the enactment of the law.

While some of these goals have been met, others have proved more elusive. The supply of vaccines was stabilized following implementation of the NVICA, albeit at a higher price (due in part to the surcharge placed on vaccines to pay for the compensation fund.) Hundreds of petitioners have received awards from the trust fund, and lawsuits filed against domestic DTP manufactuers dropped from a peak of 255 claims in 1986 to less than 20 in 1993 (CDC data). Investigational New Drug applications for vaccines have more than doubled from 1986 to 1993, possibly reflecting a more attractive commercial outlook for development of new vaccines. In the research arena there has been a very real increase in vaccine development in both public and private sectors, and particularly in the development of acellular pertussis vaccines (Jordan Report, 1995; Appendix 9).

The NVP was created to coordinate governmental and non-governmental activities related to immunization, and to allocate funds appropriated under the Act to supplement resources otherwise unavailable. The law requires that the NVP Director ensure procurement of safe and effective vaccines. The effective date of the Act was October 1988.

The National Vaccine Advisory Committee, NVAC, was established under Title XXI to serve as a technical advisory group to the NVP. The NVAC has as its mission those activities which will promote the use of vaccines, improve those vaccines already in use, and enhance the development of new vaccines.

Vaccine safety and availability are of concern to families, manufacturers, physicians, as well as the vaccines agencies of the Public Health Service (PHS). The FDA, the NIH, and the CDC are each involved in different aspects of the regulation, development, evaluation, and safe vaccine delivery. Certain aspects of vaccine supply and availability, however, are outside the current scope of the PHS. If the number of manufacturers falls, due to any reason, the possibility of a vaccine shortage can become a threat to the public health. In 1985 this became a very real possibility when the number of domestic DTP manufacturers fell to one.

APPENDIX 3

## THE POTENTIAL IMPACT OF BASIC RESEARCH AND TECHNOLOGICAL ADVANCES ON VACCINE SAFETY

The Task Force reviewed a number of examples of some basic research and technology advances which have important implications for vaccine safety. These advances offer not only challenges to the assurance of safety and a signficantly expanded scope for vaccine development, but also offer the potential for production of more pure, well characterized, consistent components and mechanism of action that the older generation of biologically active albeit effective "mixtures".

*Host Responses to Infection.* New information in the field of immunology about host responses to infection and host responses to immunization have raised important questions in regard to vaccine safety. It is now clear, for example, that recipients of the discontinued killed measles vaccine (given in the US from 1963-1967) can suffer from a potentially severe atypical measles syndrome after exposure to wild type virus or after revaccination with live attenuated virus. This syndrome is thought to be due to a delayed hypersensitivity reaction, and may be related to failure of the killed vaccine to induce antibody to the F protein of the measles virus, a recently characterized virulence factor (Markowitz & Katz, 1994). Developments in basic immunology and virology have been essential in understanding the mechanism of the atypical measles syndrome.

Another recently appreciated host response is immune enhancement. This response may have played a key role in the complications associated with an early vaccine for respiratory syncytial virus, RSV. In this situation an inactivated RSV preparation appeared to have been safe on administration, but caused some severe complications in some vaccinated children when they encountered the wild virus. The pathogenesis of immune enhancement is currently under investigation.

*Determinants of Virulence.* Attenuation, the process by which organisms lose the ability to cause disease, either through serial passage in organisms or cultures, mutagenesis and selection of auxotrophs, or by cloning of strains with virulence factor genes deleted/inactivated by mutation, is the basis of the live attenuated vaccines. Until very recently, the biologic basis of attenuation remained a mystery, and this was solely an empiric process. Moreover, because attenuation was not fully understood, the biology of reversion to pathogenicity was also unclear. This ambiguity had important implications for safety, since the genetic changes that differentiated, for example, the OPV vaccine strain from the wild virus had not been identified and could only be tested empirically (in monkeys.) This situation changed with the advent of monoclonal antibodies to viral antigens, oligonucleotide fingerprinting, and genetic sequencing technology, which can measure the extent of genetic homology among isolates, and detect subtle strain variations in genetic composition. The genetic mechanisms for virulence and attenuation have now been identified for a number of pathogens (Strebel and Sutter et al, 1992). The genetic basis for the reversion to neurovirulence of some type 3 polio vaccine strains is currently being elucidated. Genetic sequencing of mutant type 3 vaccine strains has enabled identification of transcription loci essential for viral protein synthesis (Svitkin and Cammmack et al, 1990). Research of this kind may lead to vaccine strains incapable of reversion, which could greatly reduce the incidence of vaccine associated paralytic polio, the only form of the polio seen in the US since 1980.

*Antigen Production Systems.* New technologies for the production of antigens have had important effects on vaccine safety. The two vaccines most recently added to the recommended immunization schedule for all children, the hepatitis B and *H. influenzae* type b (Hib) vaccines, are both products of the new technologies. The first hepatitis B vaccine was made from pooled hyperimmune human sera and, while efficacious and considered quite safe, it was an expensive

product with potential supply problems for mass use. Additionally there was public concern over the possibility of adventitious agents, particularly the AIDS virus. There are currently two licensed recombinant (rDNA) hepatitis B vaccines grown in yeast, the first such recombinant vaccines licensed for use in humans. This recombinant technology eliminates the need for human donors, and has produced safe vaccines with a potentially unlimited supply. Since the hepatitis antigen is produced in yeast and it is dead, there is no potential for hepatitis B infection associated with immunization.

The licensed Hib vaccines are also the product of new production technology. These are conjugate vaccines, utilizing capsular polysaccharide antigens of *Haemophilus influenzae* Type b bound to immunogenic proteins such as the outer membrane protein of *Neisseria meningitidis* or to diphtheria toxoids. These conjugates are entirely acellular, have no microbial genetic material, and have thus far had very low rates of minor adverse reactions (CDC, MMWR 1991). Conjugate vaccines are currently under development for a number of other diseases, notably against pneumococcal and meningococcal infections, and also offer the potential for promising safety profiles.

*Combination Vaccines.* One of the goals of the global Children's Vaccine Initiative (CVI) is the development of vaccines that will protect the worlds' children from a maximum number of diseases with a minimum of number of vaccinations. This is not simply a goal for developing countries. While combination vaccines such as MMR and DTP have long been in use, the recent development of new vaccines and the potential for more vaccines in the future has led to intense interest in combining antigens. The two new vaccines recently added to the U.S. universal childhood immunization schedule, Hib and hepatitis B, both require at least a three dose regimen. There is a consensus among providers that we cannot add many more visits, or many more vaccinations per visit, to achieve protection against these and other antigens without overburdening patients, parents, clinics, and the vaccine delivery system. The appeal of combination strategies becomes apparent as we consider the likely future incorporation of vaccines against varicella, rotavirus, RSV, and others, although there is always the concern that combination may enhance the rate of non-serious or serious reactions. Two formulations of a DTP-Hib combination, one combined in the syringe, have been licensed recently (Watemberg and Dagan, et al 1991). There is already considerable interest in an MMR-Varicella vaccine, MMR-V (Arbeter, Baker, and Starr, 1986; Brunell, Novelli and Lipton, 1988).

These combination vaccines will raise important challenges for the assurance of safety in addition to efficacy. There are, first, safety concerns over unsuspected adverse reactions to each of the components of these new combination vaccines. Both hepatitis B and Hib vaccines, for example, have been given to many thousands of individuals without serious adverse effects, but they had not been given to millions prior to licensure, and very rare adverse reactions are still a possibility. The evaluation of potential cross-reactions of antigens, either in the vial or in terms of the immunologic response, must also be evaluated. There remains the theoretical possibility of altered immune responses to multiple antigens given simultaneously. While the MMR and DTP combination vaccines have been efficacious, and altered immunity has not been seen with these multiple antigen vaccines, combinations of the newer classes of antigens will need to be investigated.

From an epidemiologic standpoint, the evaluation of adverse reactions to combination vaccines is complex. The methodology currently available to assess adverse events related to vaccination will need development and refinement to investigate suspected problems with combination vaccines. It may prove particularly difficult to identify specific causative components of adverse events in vaccines composed of multiple antigens. These same difficulties are likely to complicate the liability issues surrounding vaccine safety as well.

*Microcarrier Cultures.* Microcarrier cultures are continuous cell line culture systems that allow for the production of recombinant antigens on a large scale. They have been used to produce antigens of the AIDS virus (the gp160 antigen which is under evaluation as a potential HIV vaccine) in VERO cell lines, and for the production of e-IPV, OPV, and rabies vaccine in France (Montagnon, et al 1989) (Barrett, et al 1989). Microcarriers have the potential to greatly simplify the production of vaccines. The safety issues raised by this new technology are essentially the same as for vaccines produced in continuous cell lines without microcarrier technology (as explained in the section below on cell lines and vaccines).

*Vector Delivery Systems.* For many diseases the ideal vaccine is a live attenuated derivative of the disease-producing organism, which induces strong, long-lasting immune responses without causing disease. Developing such a vaccine is not always possible, however, either because the organisms cannot be cultured in the laboratory or because reliable attenuation cannot be obtained. One strategy to overcome these obstacles is to use recombinant DNA technology to insert one or more of the pathogen's genes into another organism, which then serves as a vector for expression of these genes in the host. Several of these vectors have been tested and are in various stages of development as vaccines. Safety issues may well arise with these vector vaccines, principally from the potential for reactogenicity and pathogenicity in the vector organisms.

- *Vaccinia.* Vaccinia virus, effectively utilized as the vaccine to prevent smallpox, has been extensively studied as a vector for other antigens. Because it has a large genome of approximately 200,000 base pairs, and many DNA integration sites, it has the potential for expressing multiple antigens. Antigens from influenza virus, hepatitis B, RSV, foot-and-mouth disease, malaria, rabies virus, dengue virus, HIV and human proteins, have been integrated into vaccinia. However, a number of safety issues may complicate the use of vaccinia as a vector. The vaccinia strain used to eradicate smallpox had a serious adverse reaction rate of about 1 in 50,000 doses, a rate that would be unacceptable by current standards. Adverse reactions to vaccinia included eczema vaccinatum, progressive vaccinia, generalized vaccinia, postvaccinal encephalitis, and skin lesions at the vaccination site (Henderson DA, 1994). The vaccine was contraindicated for patients with immune dysfunction, and infants with eczema (Moss, 1991). Vaccinia has the potential to produce disseminated disease in immunocompromised individuals, and a case of vaccine related disease in a patient with HIV infection has been reported (Redfield 1987). Research is now underway to develop strategies to reduce the virulence of vaccinia, and other vector viruses, through recombinant technology. A recombinant vaccinia strain has been developed which expresses the human lymphokine interleukin 2 (IL 2). This had a protective effect in immunodeficient animals, and may be an important safety advance for vectored vaccines (Andrew, et al 1991). Other lymphokine genes may also be candidates for inclusion in recombinants. Finally, other promising viral vectors without the problems inherent in vaccinia, such as canary pox virus, are being pursued.

- *Salmonella.* A variety of different Salmonella species have been studied for their potential as vaccine vectors. The rationale for this approach stems from the extensive literature on the value of attenuated salmonellae as vaccines. One currently licensed typhoid fever vaccine, Ty21a, is an attenuated strain of *Salmonella typhi.* Because these strains can be administered orally and interact with the gut-associated lymphoid tissue - where they stimulate high levels of IgA production as well as cellular immune responses - they have been most actively studied for use as vaccine vectors for diseases requiring strong mucosal immune responses. Salmonella recombinant vectors expressing the shigella O antigen, a subunit of the enterotoxin of *Escherichia coli*, and the colonization factor antigen of *Vibrio cholerae* have been tested in humans (Plotkin and Mortimer, 1988). These would all be potentially bivalent antigens, offering protection against *S. typhi* as well as the recombinant

antigen. The potential safety concerns with these vaccines include the possibility of reversion to virulence of the salmonella strains in the gut, and the well described reactogenicity of the old killed, whole cell S. typhi vaccines. As with vaccinia, recombinant technology may allow for multiple attenuating mutations to be included in vector strains, and this could increase safety and markedly decrease the potential for reversion to virulence (Hormaeche, 1991).

- *Bacille Calmette-Guèrin (BCG).* The only vaccine currently in use to prevent tuberculosis is an attenuated Mycobacterium bovis. It is the most widely used vaccine in the world, and along with HBV are the only vaccines routinely given to infants at birth. A number of BCG strains exist and while most are similar "sister" strains, others appear to differ. BCG has also been studied as a potential vaccine vector. Antigens of HIV and of Leishmania have been successfully expressed on BCG. The safety of BCG in immunocompromised individuals remains uncertain, however, and case reports of disseminated BCG disease in children with leukemia have been reported (Coppes, et al 1992). BCG is currently considered contraindicated in the US for children with HIV infection (AAP, 1991). The side effects profile of BCG in healthy recipients is also problematic, given the current demand for vaccines with very low incidence of such effects. Estimates of side effects with BCG range from 1 to 10% of recipients and include severe or prolonged ulceration at the vaccination site, regional lymphadenitis, and rarely, lupus vulgaris and BCG osteomyelitis (AAP, 1991). Clearly, recombinant vector vaccines using BCG strains as carriers will have to develop further attenuated lines of these organisms.

- *Adenoviruses.* Adenoviruses have also been used as potential vaccine vectors. Vaccine strains currently used in the military to prevent respiratory disease have been genetically engineered to express foreign DNA from respiratory syncytial virus, hepatitis B virus, and HIV. Recent studies in rats suggest that adenoviruses may be useful for delivering therapeutic gene products to patients suffering from inherited lung disorders such as alpha-1 antitrypsin deficiency and cystic fibrosis.

*Continuous Cell Lines to Produce Antigens.* Advances in biotechnology have allowed for the creation of continuous cell lines for the production of vaccine antigens. The VERO cell line, derived from monkey kidney cells, has been extensively studied in this light, and is the basis for an inactivated rabies vaccine grown on these cells and currently licensed in France, the Purified VERO Rabies Vaccine, PVRV (Merieux). This vaccine is considerably simpler and cheaper to produce than the HDCV, the human diploid cell vaccine, and it has demonstrated that VERO cells can produce large amounts of consistent and pure antigen.

*Monoclonal Antibodies and Antigenic Purification.* The development of monoclonal antibodies has revolutionized the fields of immunology and microbiology. Monoclonal technology allows for the production of highly specific antibodies to an almost limitless array of substances. In terms of antigen purification for vaccines, monoclonal antibodies can be used to detect minute amounts of undesirable protein, genetic material, and adventitious agents. This has the potential for major advances in vaccine safety. Monoclonal technology is currently being developed for use in viral protein purification, in the development of new vaccines for cholera (Sanchez and Johansen et al, 1990), leprosy (Clark-Curtis and Thole et al, 1990), respiratory syncytial virus (Baker and Wilson et al, 1992), herpes simplex (Erturk, Jennings, Phillpotts and Potter, 1991), tuberculosis (Rumschlag and Yakrus et al, 1990), malaria (Tolbert and Rupp, 1989), Chaga's disease (Segura and Cardoni, et al 1989), *H. influenzae* type b (Green and Farley, et al, 1991), and for vaccines against certain types of Hodgkin's lymphoma (Pohl and Renner et al, 1992).

*Recombinant DNA (rDNA) Techniques to Produce or express Antigens.* The application of recombinant DNA (rDNA) technology to vaccine development has led to a new generation of vaccines. The first licensed vaccine based on rDNA technology was the vaccine for hepatitis B, a yeast recombinant. Recombinant technology allows genes from one organism to be inserted into the genome of another. In the case of hepatitis B vaccine, the gene for the hepatitis B surface antigen (HBsAg) is inserted into yeast, which then express the gene product, HBsAG, on their surfaces. This antigen, after extraction and purification, serves as the active agent in the vaccine. Many more recombinant vaccines are under development and are used for recombinant "overexpression" systems where amplification genes are included in the recombinant organisms to facilitate antigen production (Sanchez J, Johanson S; Lowenadler B, 1990). Recombinant vaccines have the potential for marked advances in vaccine safety over either whole cell or live attenuated vaccines because of greatly increased purity of antigens.

*Other Delivery Systems and Routes.*

*Inhalation.* Immunization by either an inhaled or intranasal route has been investigated for a number of respiratory infections including measles and influenza. There is some basis for the concept of stimulating respiratory mucosal immunity to prevent these infections. Inhalation systems are being developed, with particular attention to consistency of dosing, patient compliance, and costs.

*Microencapsulation.* Microencapsulation holds promise for the development of "slow release" single dose immunizations that could be a major advance toward simplifying immunization schedules. However, this technology raises some important safety issues. These safety issues include adverse reactions to antigens that might not be removable from the body, sustained inclusion of solvents whose safety in encapsulated forms have not been fully investigated, and the potential for microencapsulation to lead to immune tolerance of antigens.

WHO and CVI are currently sponsoring the investigation of microencapsulated tetanus toxoid (TT) vaccines in animal systems. These would be single dose vaccines of microencapsulated antigen formulated such that antigen would be released either over a time period of weeks to months, or in two or three "pulse releases" over some months. The tetanus toxoid is encapsulated in microspheres composed of lactic and glycolic acids. A single dose of such a vaccine could potentially provide long lasting immunity to *C. tetani*. If, however, an allergic or anaphylactic reaction occurred in association with one of these vaccines, and the antigen could not be removed, sustained or pulse release could potentially lead to prolonged adverse reactions.

The solvents used in microspheres are also a potential safety problem. These solvents would also be in the body for sustained periods, might be difficult to remove or neutralize, and are not well characterized in terms of safety of long term exposure.

Immune tolerance is a theoretical safety issue with microencapsulated antigens. If an antigen is released under the correct conditions (release of small amounts over time) the immune system can become tolerant to an antigen rather than resistant to it. Immune tolerance, rather than protecting against disease, could make an individual more susceptible. The slower and more sustained antigen release of microencapsulation must be carefully evaluated to ensure that immune tolerance is not a problem with these vaccines.

A number of microencapsulation systems have been tested in animals and some have been shown to be safe and immunogenic (Moldoveanu Z, et al, 1989). A recent phase I safety and immunogenicity trial of a liposome-based micro-encapsulated vaccine against malaria evidenced both safety and impressive immunogenicity in humans (Fries, Gordon et al, 1992). It remains to be seen how large a role micro-encapsulation will play in future vaccine development.

*Devices.* The administration of vaccines, particularly multicomponent vaccines, may sometimes be best accomplished by special devices, such as multi-chamber syringes and jet injectors. These devices are often used for the multiple inoculation of individuals during an immunization campaign. FDA requires that the device and the biologic, as individual components as well as a combined product, be safe and effective prior to approval. This may complicate and slow the evaluation of products utilizing these devices. For example, issues of safety peculiar to multi-chamber syringes include consistency in mixing the components of the vaccine and consistency in volume delivered. Jet injectors, previously been associated with the transmission of infection from patient to patient, have been made safer with modification of the device itself.

*Application of Robotic Technologies to Vaccine Production.* After years of use and refinement in the auto and semiconductor industries, robotic technology has recently been applied to vaccine production. The technology offers manufacturers the advantages of increased productivity (there are reports of doubled output), consistent technique (i.e., one manufacturer is claiming over 700,000 consecutive fillings with no break in sterility), and the ability to simultaneously process batches of several products (Merck). To ensure safety, the utilization of such technology by a manufacturer will require extensive validation of the hardware and software.

## ENHANCEMENT OF IMMUNITY: THE DEVELOPMENT OF NEW ANTIGENS AND APPROACHES

It has been known for many years that the polysaccharide capsules of certain bacteria were important virulence factors in the pathogenesis of disease. Examples of these virulence factors include the Vi antigen of Typhoid, the PRP polysaccharide of *H. influenzae*, and the capsular antigens of the pneumococcus and meningococcus. It was also known that these antigens, while important in the disease process, were often poor immunogens, and evoked especially weak immune responses in children under 24 months of age. A vaccine composed entirely of one such antigen, the PRP polysaccharide of *H. influenzae* type b, though licensed in Finland, proved to be incompletely protective in American trials (Shapiro, 1990).

The immunologic basis of the response to capsular polysaccharide has begun to be understood. These antigens appear to be "T-cell independent," i.e., they fail to elicit T-cell mediated immunity, and thus to stimulate immunologic memory. The development of glycoconjugate technology allowed for the linkage of these polysaccharide antigens to more immunogenic proteins. The concept of antigen "conjugates" is that by linking protein and polysaccharide antigens, T-cell mediated, as well as humoral responses, can be elicited. The first generation of these vaccines has now been licensed; all three are conjugate vaccines of the Hib capsular polysaccharide, PRP, with immunogenic proteins such as the diphtheria toxoid or the outer membrane protein of *N. meningitidis*. These vaccines have proven to be remarkably safe and effective, and to elicit good immune responses from infants as young as 6 weeks of age (Santosham, Wolff, Reid, et al, 1991) (Black, Shinefeld, Lampert et al, 1991). Recent studies indicate that the different Hib conjugate vaccines can be safely and effectively administered in mixed sequential schedules, eliminating one safety concern.

The glycoconjugate approach should be valuable for other bacterial diseases, such as pneumococcal, streptococcal , and meningococcal diseases. A *Pseudomonas aeruginosa* conjugate vaccine has recently been tested in humans. This vaccine links a polysaccharide antigen and the Toxin A antigen of the same organism to create a novel conjugate (Schad and Lang, et al, 1991). Clinical evaluations have been done on a malaria conjugate vaccine linking an outer membrane antigen of *Plasmodium falciparum* to the pseudomonas toxin A (Cryz and Cross, et al 1991), and on an *E. coli* conjugate vaccine consisting of the O polysaccharide of *E. coli* bound to the O-PS toxin of the cholera vibrio (Fries and Gordon, et al 1992).

In addition to enhancing immunity through stimulation of both humoral and cell mediated immune responses, conjugate vaccines may have another advantage in disease prevention. There is evidence that antibody to polysaccharides alone may not cross the placenta and protect the neonate. Glycoconjugates may stimulate production of immunoglobulins that do cross the placenta, opening the possibility of maternal immunization against such important neonatal pathogens as Group B streptococcus (Baker CJ, et al. 1988).

**Approaches to Enhancing Immunogenicity** - Adjuvants

The advent of recombinant DNA technology has stimulated the production and testing of new subunit vaccines designed to be safer and more efficient. Unfortunately, the limited immunogenicity of many of these peptide or subunit candidates has hindered their development as potential vaccines, making critical various strategies to enhance their capacity to elicit a protective immune response - while avoiding the production of harmful effects. Ideally, both an improved understanding of the mechanisms of immunoenhancement and the increasing number of experimental approaches available should be integral components of rational vaccine design. The process of development of new vaccines, however, is still highly empirical.

Adjuvants are agents which make it easier for an antigen to elicit an immune response. Depot-type adjuvants, such as alum, were originally thought to increase the immunological half-life of the antigen, but their effects may be mediated by cytokine release (Allison, 1992). Novel adjuvants may function by one of the following mechanisms: 1) changing the conformation of the antigen, thereby enhancing the antigen presentation; 2) preventing proteolytic destruction in the stomach, thus allowing the antigen to pass into the intestines intact for presentation to gut-associated lymphoid system; 3) targeting antigen directly to M cells of the gut to induce mucosal immune responses; 4) targeting macrophages (particulate adjuvants); and 5) inducing the production of various immunomodulatory cytokines, which act directly on thymus-derived helper (Th) lymphocytes to selectively promote specific arms of the immune system.

The traditional approach to vaccine development assumes that a vaccine will stimulate an immune response that is qualitatively and quantitatively similar to that produced by natural infection, and that this will prevent disease when a person is subsequently exposed to the pathogen. Often, the immune response after vaccination is far weaker than that measured after disease, and protection can be variable. Adjuvants are substances that can amplify the cell-mediated and humoral immune response to an antigen. The only adjuvant approved for human use in the U.S. is aluminum salt (aluminum hydroxide or aluminum phosphate) which when adsorbed to antigen augments antibody responses to diphtheria and tetanus toxoids and the hepatitis B vaccines. Vaccines containing alum adjuvants, however, can not be lyophilized or frozen, are not effective with all antigens, and fail to stimulate cell-mediated immunity.

The development of alternative conventional vaccine adjuvants is approached empirically by mixing an antigen with the potential adjuvant, and must be tested in an animal or human to determine effectiveness and safety. Research in this area is focused on oil-based emulsions that contain biodegradable materials. Candidates include the Syntex formulation SAF-1 (containing squalene oil, an amino acid derivative of muramyl dipeptide [threonyl-MDP], and nonionic block polymers), the Ciba-Geigy formulations (containing squalene, surfactants, and a fatty acid derivative of muramyl tripeptide [MTPPE]), the Ribi formulation (containing monophosphoryl lipid A and mycobacterial cell walls), and the saponin derivatives, such as the Cambridge Biotech QS21.

The development of new adjuvants has been dominated by concerns regarding safety (Goldenthal KL 1993). Some of these have begun early trials in humans, while others are being developed for

veterinary vaccines. Some of the empirically developed adjuvants have been too toxic for use in humans, causing tissue damage at the site of injection and later granulomatous reactions, pyrogenicity, arthritis and anterior uveitis. While effective adjuvants can reduce the amount of foreign proteins introduced in the vaccinee by achieving protection with fewer doses, the extensive experience with the adverse reactions caused by candidate adjuvants prompts FDA to demand an approach to testing for safety which is even more careful and systematic than that required for a new antigen. Prudently, the preclinical animal safety studies will use the exact antigen-adjuvant combination, routes of administration, injection volume and formulation intended for clinical use to best demonstrate freedom from untowards events.

**Approaches to Enhancing Immunogenicity** -- Epitope-Based Strategies

Strategies for immunization with only the relevant epitopes have developed as a result of an enhanced understanding of the mechanisms for antigen recognition by B and T cells. Theoretically, these strategies result in an immune response only to the relevant target, and offer the potential for avoiding the toxicity associated with the presence of an immune response to other components of the pathogen. The simplest approach is to link B cell and T cell (helper and cytotoxic) epitopes and use these linear poly-epitopes as vaccines. In practice, a good humoral immune response may be elicited, but genetic restrictions may limit the ability to mount an appropriate response to these immunogens. How to optimize the arrangement of epitopes and how to present antigens to the immune system in a manner that maintains conformational and functional integrity (i.e., either as synthetic peptides or as expressed peptides in vectors such as vaccinia virus) has not yet been determined, but is currently under active investigation in a number of laboratories. Although epitope-based approaches stimulate good antibody responses, they do not stimulate potent cellular immunity, especially cytotoxic T cell responses.

Therefore, other approaches are being pursued. One interesting approach is the use of Multiple-Antigen Peptide Systems (MAPS) which consist of selected T and B cell epitopes that are conjugated to a polylysine core without a carrier protein (Lu, 1991; Chan et al, 1992). MAPS are structurally defined, contain a quantifiable amount of well characterized, pure antigen, can be administered intraperitoneally and generate antibodies with high specificity. This approach has been applied to the development of totally synthetic vaccines for HBV, malaria, and HIV infection (Hordelli, 1993).

Genetic fusion of immunogenic peptides with the nontoxic B subunit of cholera toxin functions as an adjuvant for inducing mucosal immune responses. This combination targets the Peyer's patches in the intestine and results in a brisk, sustained immune response to the attached peptide sequence. Nontoxic derivatives of cholera toxin (and the related *E. coli* heat/-labile toxin) are also being evaluated.

**Approaches to Enhancing Immunogenicity** -- Particulate Antigens

Liposomes and microspheres can protect antigens from proteolytic destruction in the stomach, allowing antigen to pass into the intestines intact for presentation to gut-associated lymphoid tissue. Different types of liposomes have been tested over the past 20 years. Recently, immunostimulating reconstituted influenza virosomes (IRIVs), spherical, unilamellar vesicles that combine the hemagglutinin membrane glycoprotein of the influenza virus with antigen have been tested in a hepatitis A vaccine formulation in humans.

Microcapsules consist of an inner reservoir of antigen surrounded by an outer biodegradable polymer wall (most recently lactide-*co*-glycolide polyesters) which slowly release antigen in the lymphoid tissue. The technology has been available for 30 years, but has been explored with

vaccines only recently. The composition and size of microcapsules are varied, and produce high, sustained immune responses to toxoids and viral antigens. Although the microcapsules consist of the same material used to make resorbable sutures, the possibility of adverse reactions to a slow release allergen remains a safety concern, albeit a theoretical one at this point. Because microcapsules between 5μm and 10μm in diameter are taken up by the Peyer's patches of the gastrointestinal tract, oral administration of microspheres has been shown to effectively elicit immune responses in mice. The effectiveness of this approach will require careful evaluation, because although microcapsules maintain the peptide in the dry state, avoiding the need for a cold chain, the process does expose antigens to organic solvents, thereby decreasing immunogenicity .

Another approach has been to incorporate antigens into solid particles called ISCOMs (immunostimulatory complexes). These structures are generated by mixing antigen with the detergent Quil A. The ISCOM self-assembles into stable 35 nm cage-like structures held together by the hydrophobic interactions between the matrix (Quil A), added lipids, and the antigen. ISCOMs containing viral membrane proteins have been tested in animals and found to stimulate 10-fold increases in antibody compared to controls. When complexed with glycoprotein, ISCOMs may also induce cytotoxic T cell responses, perhaps through the delivery of antigen directly to the cytosol for presentation with MHC class I molecules. Cytosolic antigen delivery by membrane-active adjuvants mimics the antigen presentation that occurs during viral infection or after immunization with live-attenuated vaccines.

Protein cochleates, which are stable protein-phospholipid-calcium precipitates, represent recent and novel formulations to enhance the immunogenicity of antigens. The name derives from their unique structure, a rolled up lipid bilayer maintained by calcium bridges. Membrane proteins or peptides with lipid anchors can be integrated into this lipid bilayer, which, when rolled up, protects them from intestinal acid and allows them to be slowly taken up by the Peyer's patches. They can, thus, serve as efficient methods for multiple antigen presentation, and stimulate strong circulating and mucosal antibodies which protect against infection upon challenge in the mouse model. This approach is currently being tested with influenza, parainfluenza and HIV vaccines.

### Cytokines

An emerging area of immunologic enhancement involves the use of cytokines to direct and boost immune responses. $CD4^+$ T-helper lymphocytes have been subdivided into two classes depending on the pattern of cytokines they produce, Th1 and Th2 responses. Th1 cells are prominently involved in cell-mediated immunity and produce cytokines such as Interleukin-2 (Il-2) and interferon-γ (IFN-γ), whereas Th2 cells help antibody production and produce cytokines such as Il-4 and Il-10. In certain chronic infections, such as leishmaniasis or schistosomiasis, whether the predominant immune response is Th1-like or Th2-like determines the severity of disease. In principle, therefore, the ability to manipulate the immune response towards a Th1- or Th2-like response may permit one to enhance immunologic protection and minimize immunopathology.

IL-12 is a recently characterized cytokine that may play a pivotal role in immunomodulation. The adjuvant activity of IL-12, when given with antigens, has been demonstrated in a leishmania vaccine in mice. Immunization of BALB/c mice with *Leishmania major* antigens and IL-12, induced leishmania-specific CD4+ Th1 cells that conferred protection against *L. major*. Immunization of control animals with antigen alone elicited Th2-type immune responses that were not protective.

### Nucleic Acid Vaccines

The injection of relatively simple DNA-containing bacterial plasmids into muscle of mice has been shown to result in expression of genes encoded by the plasmid. This approach has recently been named "nucleic acid vaccines" by the World Health Organization, and is receiving much attention for several reasons. First, such vaccines appears to be capable of stimulating both humoral and cell-mediated immune responses. After a single dose of this type of vaccine, IgG antibodies have been shown to increase for 1-2 months, and then either remain stable or gradually fall. Furthermore, cellular immunity has been induced, with both effective priming and boosting observed in mice. The duration of the immune response is observed for at least 19 months after injection. Second, the route of administration may be parenteral, mucosal or via a gene-gun that delivers tiny amounts of DNA-coated gold beads. Finally, this strategy results in relevant antigen production in primates without the use of infectious agents. Thus, this approach to vaccine development is relevant to a number of diseases, including HIV, and can be expected to continue to receive intense scrutiny. Evaluation of safety of this approach will be central to its safe development and testing in humans.

## APPENDIX 4
### New and emergent infectious diseases: unexpected challenges to vaccinology

In the last decade several new or previously unidentified infectious diseases have been recognized as important pathogens. A number of these diseases are currently the subject of intensive vaccine research. The causative agent of Lyme disease, the spirochete *Borrelia burgdorferi*, was identified less than ten years ago. Lyme disease is now the most common vector-borne disease in the United States, with several highly endemic regions recognized. HIV, the human retrovirus which is the causative agent of AIDS, has now taken the lives of over 200,000 Americans. The disease was first identified in the US in 1981, and has since become a global pandemic. In the last 2 years, 7 outbreaks of Multi-Drug Resistant *Mycobacterium tuberculosis*, MDRTB, have occurred in US hospitals and prisons. These antibiotic resistant Tb strains are challenging to treat and represent a new and potentially life-threatening occupational hazard for health care workers, correctional facility staff, and staffs of shelters and service agencies for the homeless, as well as an important nosocomial risk for any hospitalized patient.

Each of these three diseases has presented major challenges to vaccine research. The development of a safe and effective vaccine against HIV is now an international effort. HIV is the first human retrovirus for which vaccine development has been attempted. The current candidate HIV vaccines illustrate the application of biomedical advances to vaccine development; they employ transformed cell lines, recombinant antigens and vectors, ISCOM (immunostimulatory complexis) technology, and monoclonal antibody assays. A number of HIV vaccines have been tested in HIV-infected patients, and a therapeutic role for these vaccines is a potential benefit of HIV vaccine research. Clearly, an important concern with any HIV vaccine is adventitious transmission of the HIV virus. Development of such vaccines is challenged by concerns over lack of efficacy, transmission of the AIDS virus or any part of its genome and production of high titers of antibody against an immunodominant, non-neutralizing epitope. The public's concern over these issues may be barrier a to the clinical testing of HIV vaccines and to their acceptance.

The Lyme Disease agent is the first tick-borne spirochete for which intensive vaccine research has been done. Vaccines for Lyme Disease have been tested in humans, and an animal vaccine has shown protection in mice, one of the principal host species of the organism. Research is now focused on characterizing the immune response to the *B. burgdorferi*, identifying the antigenic determinants of the organism, and on understanding the transmission of the disease to humans. The answers to these basic research questions will be essential in the development of safe and effective vaccines for Lyme disease.

While there is a vaccine for Tb, BCG, its efficacy in adults is uncertain for any indication, and its efficacy in children is controversial, but generally agreed to be limited to the prevention of extrapulmonary complications of Tb infection such as tuberculous meningitis or osteomyelitis (MMWR, 1988). Clearly, new Tb vaccines are an urgent research priority. The BCG vaccine, one of the oldest vaccines in use, contains a live attenuated organism. The new generation of Tb vaccines will undoubtedly employ new strategies, and efforts are already underway to create safer and more effective acellular, recombinant, and epitope vaccines that will protect against Tb infection while preserving the usefulness of Tb skin testing, with which BCG interferes.

The emergence/reemergence of these infectious diseases points to the need for continued epidemiologic and basic research in infectious diseases, as well the development of vaccines to control and prevent disease in the future.

## APPENDIX 5
### The laboratory evaluation of vaccine safety

*Polymerase Chain Reaction (PCR).* PCR is a new technology for detecting the presence of genetic material. PCR works on the principal of gene amplification, so that previously undetectable amounts of nucleic acid, if present in a sample, can be chemically amplified and detected. Because of its extreme sensitivity PCR represents a major improvement in the ability to detect small amounts of nucleic acid which could not have been detected with earlier methods; thus its application to vaccines may represent an advancement in the assessment of vaccine purity. PCR can be used to rapidly identify, clone, and sequence microbial genes responsible for disease, abilities which may have important applications for vaccine development as well as safety. The likelihood of adventitious viral agents in vaccines, or of such agents in vaccines grown in tissue culture, could be substantially reduced by the use of PCR. In addition, PCR is able to detect short segments of altered genetic material. With this capability PCR has been used to detect altered nucleotide sequences in polio vaccine strains which correlated with reversion to neurovirulence. In one experiment, neurovirulent strains which had passed undetected in the intraspinal monkey neurovirulence test were detected by PCR (Chumakov and Powers et al, 1991). This finding could be of considerable importance and presents one approach to decreasing the risk of vaccine-associated polio.

*Transgenic animals.* There have long been theoretical and practical challenges to the extrapolation of animal model immune responses to human diseases. In terms of vaccines, especially for those diseases where animal models are problematic or non-existent, the evaluation of safety, immunogenicity, and antigenicity has been difficult. The use of transgenic animals and the development of animal models with genetically altered immune systems has improved this situation considerably. Before the development of a transgenic mouse model, the only animal model for evaluating the polio vaccine strain and its potential for reversion to neurovirulence was the intraspinal injection model in monkeys. This monkey model was expensive, and because it did not involve the gut, less than ideally suited to the evaluation of human disease. The transgenic mouse model offers promise of an improved system for the evaluation of this important vaccine safety concern.

*Informatics revolution.* The cross-reactivity of vaccine antigens with human proteins has been considered a potential threat to the safety of vaccination. In theory, if vaccines induce antibody to proteins which have cross reactivity with human proteins, these induced antibodies could cause immune-related disease states. This concern has been raised in regard to vaccines against *Streptococcus pneumoniae* type 14, Group B streptococcus (GBS) and *N. meningitidis.* Certain antigens of the type 14 pneumococcus may share epitopes with human red blood cell membranes. Polysaccharide units of GBS share sugar structures with human glycoproteins (Hayrinen, Pelkonin and Finne, 1989). And there is some evidence of antigenic similarity between the meningococcus and antigens of developing neural tissue (Finne, Leinonen and Makela, 1983). At present these potential examples of cross-reactivity are all theoretical, and there is little evidence that such antigenic similarities are of clinical significance. But the ability to identify and sequence antigen genes which may cross react with human proteins could greatly reduce the possibility of "auto-immune" or immune-complex complications of vaccination. The informatics revolution, which has resulted in powerful computer systems that facilitate multiple comparisons and storage of information, has greatly improved the sensitivity of these investigations, and allows for comparisons of human and microbial gene sequences, as well as their amino acid and glycoprotein products.

*Control of Manufacture and Release.* Improvements in the safety of vaccines in use today has also been the goal of widespread promulgation of standards for Good Laboratory Practices (GLP) and current Good Manufacturing Practices (cGMP) by the pharmaceutical industry. These standards

have been used to upgrade and standardize the procedures used in the manufacture of all vaccines in the United States. However, although WHO has issued guidance documents on manufacture and control authorities, consistent high standards are not used world-wide. The manufacturers, working with the FDA, are currently collaborating with the International Conference on Harmonization to harmonize requirements and establish a higher set of standards for ensuring vaccine safety. Harmonized preclinical testing standards will enable international test data to be used in the FDA review and licensure process, thereby facilitating the availability of foreign-manufactured vaccines in the U.S.

## APPENDIX 6
### Evolving recommendations for the use of vaccines.

Measles A single dose of live measles vaccine had been recommended since measles vaccine was first licensed. In 1963 the recommended age for vaccination was 9 months; in 1965 the age was changed to 12 months. In 1976 the recommended age was changed again to 15 months of age because vaccine efficacy was found to be lower in persons vaccinated at 12-14 months of age.

The recent measles epidemic in the U.S. was principally due to failure to immunize children at appropriate ages; this led to low coverage levels particularly in high risk groups (JAMA, 1991). However, even prior to the 1989-1990 outbreaks, immunization strategies were being evaluated due to random measles outbreaks predominately among school-aged children. Studies of the transmission patterns in the U.S. during the period 1985-1986 described two major types of outbreaks; those among preschoolers (26%) and outbreaks among school-aged children (67%). Investigation of the outbreaks among highly vaccinated school-aged children revealed that vaccination between 12-14 months was a risk factor for the outbreaks. However, investigation of the pre-school outbreaks revealed that the national measles elimination strategies were functioning suboptimally, in that a large number of cases were occurring in un-vaccinated, vaccine-eligible children 16 months to 4 years of age. A variety of policy changes were considered at that time, one of which was a routine 2 dose schedule which would be expected to reduce the number of primary vaccine failures and potentially raise immunity levels to above 95 percent (Markowitz, 1989).

The next series of measles outbreak investigations occurring during the 1989-1990 period revealed other important factors to consider in making further policy changes. Investigations of those outbreaks demonstrated that a variety of financial and situational barriers existed to receiving immunizations, and that opportunities were frequently missed to assess the vaccination status of children when services were delivered for reasons other than the well baby check-ups.

Important consequences of the 1985-1986 and 1989-1990 measles epidemics were that the ACIP re-evaluated current measles dosage and schedule recommendations. The resulting ACIP recommendations called for a routine two-dose schedule, both doses preferably given as combined MMR. The first dose was recommended to be given at 15 months but at 12 months in recurrent measles transmission areas, since outbreaks were continuing in the less than 15-month age group. The second dose was recommended at 4-6 years unless the geographic area is considered high risk. A subsequent recommendation required documentation of receipt of 2 doses after the first birthday or other evidence of measles immunity for individuals in post-high school settings such as college, and persons beginning training in the medical field.

One of the findings from the recent measles investigations was that many practitioners were failing to age-appropriately immunize due to what are considered false contraindications such as mild respiratory illness. Thus, as another important consequence of the 1989-1990 measles epidemics, the NVAC recommended standards of immunization practice which set forth true versus false contraindications for administering all mandatory childhood vaccines. The standards for both the private and public sector were developed by the CDC in consultation with a diverse group of relevant interested parties and were subsequently adopted by the advisory groups. These include standards for assuring that vaccine is administered safely.

Most recently, the ACIP has examined evidence for the decreasing level of antibody in the cohort of young mothers that have obtained protection from vaccine. As a result, the recommended age for administration of the first MMR has been dropped to 12 months.

Pertussis. Work has been on-going for over 20 years to identify and purify the antigens of *Bordetella pertussis* that can be incorporated into acellular vaccines that are protective but less reactogenic than whole-cell vaccines. The concern over reactogenicity has been more prevalent in some countries than others. Industry enthusiasm for the development of a vaccine that would replace an already licensed, effective vaccine required encouragement from the PHS. In Sweden, acellular pertussis vaccines were evaluated previously in infants and although clinical vaccine efficacy was considered good, the estimates were not considered superior to estimates that were previously obtained for whole-cell vaccine (there was not a concurrent whole cell arm in this trial). Thus, the data did not result in licensure of acellular pertussis vaccine for infants in the U.S. or Sweden. In 1991, the immunogenicity and safety of 13 acellular products were compared to whole-cell vaccine in a multicenter, randomized, double-blinded study in over 2,400 U.S. infants conducted at six NIAID Vaccine Evaluation Units. The trial demonstrated that most of the acellular products were of equal or superior immunogenicity compared to whole-cell vaccine (Decker et al, 1995). Without a serologic correlate of protection, however, immunogenicity data can not be used for conclusive determination of efficacy.

The Phase III efficacy trials in Sweden and Italy demonstrated excellent safety and efficacy compared to U.S. whole cell vaccine in 1995. Other efficacy trials are currently in progress. Until these vaccines are licensed for infants, the ACIP has continued to recommend that whole-cell pertussis vaccine be given for the primary series in infants, and acellular pertussis vaccine for the fourth and fifth doses. This recommendation will remain unless and until an acellular pertussis vaccines have been licensed for infants.

None of the clinical trials, however, will have the statistical power to demonstrate an association, should it exist, between acellular pertussis vaccines and serious but rare neurologic adverse events. Therefore, other approaches to determine causality, such as Large Linked Databases, must be used (see Appendix 7).

Hepatitis B. The reported incidence of acute hepatitis B (HBV) increased 37% between 1979 and 1989. It is estimated that approximately 1.25 million persons with chronic HBV infection in the U.S. are potentially infectious to others. In the past, the recommended strategy for preventing infection has been to vaccinate high risk groups only. It has been recognized that this strategy alone in the U.S. is insufficient since it is difficult to identify high risk persons and vaccinate such persons prior to infection, and also because many already infected individuals continue to infect others through their lifestyles, behaviors, and/or occupations. Transmission patterns which tend to vary geographically have made the disease very difficult to control.

The failure of past strategies to reduce disease transmission and the resulting increase in incidence of disease prompted the recent recommendation to vaccinate all infants as part of a routine universal vaccination schedule to promote a comprehensive approach to elimination of disease transmission. Initially, the recommendation for universal HBV vaccination was not widely distributed to private practitioners; many physicians were not aware of the new recommendations, and others did not agree with the recommendation for immunizing all infants with HBV vaccine (Freed et al 1993). Recent CDC initiatives have addressed the education of both health care professionals and the public, and new vaccine policies address the financial barriers to effective adoption of new immunization recommendations for HBV. Finally, combination vaccines in development will address the perceived deterrent of multiple injection at single visits.

## APPENDIX 7
## Assessing the Causality of Adverse Medical Events Following Vaccination: Large-Linked Databases

A person is vaccinated and experiences an adverse medical event in the following days. Did the vaccine cause the adverse event - is it a true reaction? If it happens frequently to a number of people in the few days after immunization with one vaccine, laboratory results define the vaccine as the cause, or the patient develops an unique clinical syndrome attributable only to the vaccine, this question will be readily evaluated and answered. However, if the event is extremely rare, and occurs frequently in response to other stimuli, then the question turns out to be difficult to answer. This is especially important when the "medical event" is life threatening or causes permanent damage, because this will lead both the individual as well as the public health system to reevaluate the risks and benefits of the vaccine.

The clinical studies required before vaccines are licensed by FDA demonstrate vaccine safety and efficacy. However, for financial and logistical reasons, phase III trials generally are limited to less than 10,000 children, more often several thousands of children. It is obvious that these carefully controlled studies will not be able to answer questions of causation for very rare adverse events - on the order of 1/100,000 children. In addition, universal immunization programs make it difficult to find people who are similar except for their vaccination status. Because lack of immunization is not random, univaccinated people are likely to differ in other ways that are related to the outcomes of interest.

The creation of linked systems of information derived from hospital charts, clinic charts and immunization records - "large linked databases" (LLDB) - are a recent innovation made possible by powerful and available computers. In 1990, the CDC/NIP funded an LLDB called the Vaccine Safey Datalink to monitor vaccination and rare adverse reactions. The VSD links computerized records from four large group health plans, creating a database of medical records which include vaccinations, hospital discharge diagnoses, emergency room visits, other outpatient medical care, and other ancillary information. The population under active surveillance numbers over 0.6 million, and is comprised of children during their first 7 years of life. This is roughly 2% of the U.S. population in this age range.

### Vaccine Safety Datalink (VSD)

Development of the VSD makes the conduct of observational studies in very large populations possible to help determine plausible associations between vaccines and rare adverse events. The VSD is the first LLDB study in the U.S. with large enough population to study rare events routinely. Table 2 identifies health outcomes that are being evaluated for an association with respective vaccines.

Having identified those people with the illness, treatment, or test of interest, the VSD system links this information with their immunization record, allowing a comparison of the frequencies of recent vaccination (e.g., within 7 days) with those of similar people (age, gender, ethnicity) without this illness. Another approach is to compare the rates of the illness/condition of interest to other groups that are otherwise similar, differing only in timing of their immunization.

The first fifteen months of investigation fail to show, with a few exceptions, any associations between the studied outcomes and vaccination. Several relatively common outcomes were found to be associated with vaccination, among them seizures with DTP and MMR (table 2). The risk of seizure on the same day as DTP vaccination was 3 times higher than children who had not had a

documented vaccination within 30 days. Similarly, the relative risks of seizures within 4-7 and 8-14 days following receipt of MMR were 2.7 and 3.3, respectively.

Many factors suggest that these seizures are related to fevers. These include the tendency of children to have high fevers and febrile seizures, DTP's ability to cause fever compared to MMR's side effect of mild illnesses. A nested study of conventional medical records is now in progress. The risk of any seizure event, particular types of seizures, and newly diagnosed seizure disorders, will be examined for each vaccine independently, and for various combinations of simultaneously-administered vaccines. Results may improve the safety of vaccines by using fever-controlling medications with certain vaccinations. This practice may reduce the possibility of fevers, fever-associated seizures, and related health sequela in young children.

**Challenges of LLDBs**

Despite the size of the LLDB database (over 0.6 million children), there are not enough cases of some rare adverse events to be evaluated. For instance, aseptic meningitis cases are rarely documented after receipt of the MMR, OPV, Hib, DTP, and HEP vaccines. The numbers of cases were so few (<15 cases for each vaccine), that it is impossible to tell if the vaccine was associated with aseptic meningitis, or if these cases happened by chance.

Vaccines are almost always co-administered with other needed vaccines, making determination of causation by a given vaccine very difficult. Also, vaccine combinations will vary depending on the needs of the client, preference of the health care provider, and state policies. For instance, of the total 324,500 OPV vaccines provided, only 3,631 were given alone. The rest were given in some combination that may have included DTP, MMR, Hib, and HEP.

The VSD is typical of LLDBs in that most of the records being screened were automated for administrative or clinical purposes, and quality may not meet scientific standards. For many reasons, all medical charts must be reviewed by VSD staff. Record reviews have also helped in identifying cases though use of ancillary information, (b) (5)

**Future Plans**

(b) (5) By October, 1995, 800,000 more records will be available. (b) (5)

By enlarging the LLDB, it will be possible to evaluate some rare adverse events, including aseptic meningitis, thrombocytopenia (decreased clotting cells in blood), seizures, and other neurological outcomes. Other issues to be investigated include the risks of vaccinating children with various illnesses, and the implications of simultaneous vaccinations. The latter is particularly important with the introduction of varicella, and other new vaccines. Completing these projects will require extensive coordination efforts among CDC, FDA, and the investigators involved in managing the LLDB. Results may affect recommendations regarding vaccine schedules, combinations, and policies for new vaccines.

## Table 2
## Vaccine Safety Datalink Project
## Vaccines and Conditions whose Associations are being Evaluated

| CONDITIONS | VACCINES |
|---|---|
| **Neurologic** | |
| Aseptic Meningitis | DTP, OPV, MMR |
| Increased Intracranial Pressure | DTP |
| Encephalitis and Encephalopathy | DTP, MMR |
| Ataxia | MMR |
| Seizures and Persistent Seizure Disorders | DTP, MMR |
| Reye's Syndrome | DTP |
| Transverse Myelitis | DTP, OPV, MMR |
| Guillain-Barré Syndrome | DTP, O-IPV, MMR, HbCV-PV |
| Cranial Nerve Disorders | DTP |
| Peripheral Nerve Disorders | DTP, MMR, IPV |
| Hearing Loss | MMR |
| Polio and Acute Paralytic Syndromes | OPV |
| **Allergic** | |
| Anaphylaxis | DTP, O-IPV, MMR, HbCV |
| Asthma and Bronchitis | MMR |
| **Hematologic** | |
| Hemolytic Anemia | DTP |
| Thrombocytopenia | DTP, MMR |
| **Infectious and Inflammatory** | |
| Diarrhea | DTP, MMR |
| Invasive Bacterial Disease | DTP, HbCV-PV |
| Autoimmune and Immune Complex Diseases | DTP, MMR |
| Vaccine-Preventable Diseases | DTP, MMR, HbCV-PV |
| Other Infections | DTP, MMR |
| Myocarditis | MMR |
| Pancreatitis | MMR |
| Parotitis | MMR |
| Arthropathy and Arthritis | MMR |
| **Metabolic** | |
| Hypoglycemia | DTP |
| Diabetes | MMR |
| **Other** | |
| Site Abscesses | DTP |
| Persistent Crying | DTP |
| Collapse--Hypotonic, Hyporesponsive Episodes | DTP |
| Breath Holding | DTP |
| Sudden Infant and Other Unexpected Deaths | DTP |
| Apnea | DTP |
| Adverse Events | All |

Vaccines and their Acronyms:

Diphtheria and Tetanus toxoids and Pertussis vaccine (DTP)
Measles, Mumps and Rubella live-viral vaccine (MMR)
Oral (OPV) and Inactivated (IPV) Poliovirus Vaccines
Haemophilus influenzae type b Conjugate (HbCV) and Polysaccharide Vaccines (HbPV);
All includes Hepatitis B Vaccine (HBV), Varicella Vaccine (trade name VARIVAX)
and any others that are included in the childhood vaccination schedule

(b) (5)

Appendix 8

## APPENDIX B
## Summary of Conclusions From Institute of Medicine Study of Adverse Effects of Pertussis and Rubella Vaccines

| Conclusion | Adverse Event Reviewed | |
|---|---|---|
| | DPT Vaccine[1] | RA 27/3 Rubella Vaccine[2] |
| 1. No evidence bearing on a causal relation[3] | Autism | |
| 2. Evidence insufficient to indicate a causal relation[4] | Aseptic meningitis<br>Chronic neurologic damage<br>Erythema multiforme or other rash<br>Guillian-Barré syndrome<br>Hemolytic anemia<br>Juvenile diabetes<br>Learning disabilities and attention deficit disorder<br>Peripheral mononeuropathy<br>Thrombocytopenia | Radiculoneuritis and other neuropathies.<br>Thrombocytopenia purpura |
| 3. Evidence does not indicate a causal relation[5] | Infantile spasms<br>Hypsarrythmia<br>Reye Syndrome<br>Sudden Infant Death Syndrome | |
| 4. Evidence is consistent with a causal relation[6] | Acute encephalopathy[7]<br>Shock and 'unusual shock-like state' | Chronic arthritis |
| 5. Evidence indicates a causal relation[8] | Anaphylaxis<br>Protracted, inconsolable crying | Acute arthritis |

Source: Institute of Medicine. *Adverse Effects of Pertussis and Rubella Vaccines: A Report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines.* National Academy Press, Washington, D.C., 1991.

[1] Evidence does not differentiate between DPT vaccine and the pertussis component of DPT vaccine except in the case of protracted, inconsolable crying where the evidence implicates the pertussis component specifically.

[2] RA 27/3 MMR, Trivalent measles-mumps-rubella vaccine containing the RA 27/3 rubella strain.

[3] No category of evidence was found bearing on a judgement about causation (all categories of evidence left blank in Table 1-1

[4] Relevant evidence in one or more categories was identified but was judged to be insufficient to indicate whether or not a causal relation exists (no category of evidence checked as supporting causation in Table 1-1: exceptions are this designation under biologic plausibility for erythema multiforme and hemolytic anemia)

[5] The available evidence, on balance, does not indicate a causal relation (one or more categories of evidence checked as not supporting causation in Table 1-1, with evidence supporting causation being either absent or outweighed by other evidence)

[6] The available evidence, on balance, tends to support a causal relation (one or more categories of evidence checked as supporting causation in Table 1-1, with evidence checked as insufficient or not supporting causation being absent or outweighed by the other evidence)

[7] Defined in controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis.

[8] The available evidence, on balance supports a causal relation, and the evidence is more persuasive that in level 4 above (the categories of evidence are coded similarly to 4 above, with evidence checked as insufficient or not supporting causation in Table 1-1 being absent or fewer than in level 4)

**TABLE 1-2** Conclusions Based on the Evidence Bearing on Causality

| DT/Td/T | Measles[a] | Mumps[a] | OPV/IPV[b] | Hepatitis B | *H. influenzae* type b |
|---|---|---|---|---|---|
| ***Category 1: No Evidence Bearing on a Causal Relation*** | | | | | |
| | | Neuropathy | Transverse myelitis (IPV) | | |
| | | Residual seizure disorder | Thrombocytopenia (IPV) | | |
| | | | Anaphylaxis (IPV) | | |
| ***Category 2: The Evidence Is Inadequate to Accept or Reject a Causal Relation*** | | | | | |
| Residual seizure disorder other than infantile spasms | Encephalopathy | Encephalopathy | Transverse myelitis (OPV) | Guillain-Barré syndrome | Guillain-Barré syndrome |
| Demyelinating diseases of the central nervous system | Subacute sclerosing panencephalitis | Aseptic meningitis | Guillain-Barré syndrome (IPV) | Demyelinating diseases of the central nervous system | Transverse myelitis |
| Mononeuropathy | Residual seizure disorder | Sensorineural deafness (MMR) | Death from SIDS[c] | Arthritis | Thrombocytopenia |
| Arthritis | Sensorineural deafness (MMR) | Insulin-dependent diabetes mellitus | | Death from SIDS[c] | Anaphylaxis |
| | Optic neuritis | Sterility | | | Death from SIDS[c] |
| Erythema multiforme | Transverse myelitis | Thrombocytopenia | | | |
| | Guillain-Barré syndrome | Anaphylaxis[d] | | | |
| | Thrombocytopenia | | | | |
| | Insulin-dependent diabetes mellitus | | | | |
| ***Category 3: The Evidence Favors Rejection of a Causal Relation*** | | | | | |
| Encephalopathy[e] | | | | | Early onset *H. influenzae* b disease (conjugate vaccines) |
| Infantile spasms (DT only)[f] | | | | | |
| Death from SIDS (DT only)[f,g] | | | | | |
| ***Category 4: The Evidence Favors Acceptance of a Causal Relation*** | | | | | |
| Guillain-Barré syndrome[h] | Anaphylaxis[d] | | Guillain-Barré syndrome (OPV) | | Early-onset *H. influenzae* b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine |
| Brachial neuritis[h] | | | | | |

*continued*

**TABLE 1-2** *(continued)*

| DT/Td/T | Measles[a] | Mumps[a] | OPV/IPV[b] | Hepatitis B | *H. influenzae* type b |
|---|---|---|---|---|---|
| *Category 5: The Evidence Establishes a Causal Relation* | | | | | |
| Anaphylaxis[d] | Thrombocytopenia (MMR) | | Poliomyelitis in recipient or contact (OPV) | Anaphylaxis | |
| | Anaphylaxis (MMR)[d] | | | | |
| | Death from measles vaccine-strain viral infection[c,j] | | Death from polio vaccine-strain viral infection[c,j] | | |

[a]If the data derive from a monovalent preparation, then in the committee's judgment the causal relation extends to multivalent preparations. If the data derive exclusively from MMR, that is so indicated by (MMR). In the absence of any data on the monovalent preparation, in the committee's judgment the causal relation determined for the multivalent preparations does not extend to the monovalent components.

[b]For some adverse events, the committee was charged with assessing the causal relation between the adverse event and only oral polio vaccine (OPV) (paralytic and nonparalytic poliomyelitis) or only inactivated polio vaccine (IPV) (anaphylaxis and thrombocytopenia). If the conclusions are different for OPV than for IPV for the other adverse events, that is so noted.

[c]This table lists weight-of-evidence determinations only for deaths that are classified as SIDS and deaths that are a consequence of vaccine-strain viral infection. However, if the evidence favors the acceptance of (or establishes) a causal relation between a vaccine and an adverse event, and that adverse event can be fatal, then in the committee's judgment the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a vaccine-associated adverse event is limited to tetanus-diphtheria toxoid for adult use (Td) and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and OPV and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and *H. influenzae* type b unconjugated PRP vaccine and early-onset *H. influenzae* type b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See Chapter 10 for details.

[d]The evidence that establishes a causal relation for anaphylaxis derives from MMR. The evidence regarding monovalent measles vaccine favors acceptance of a causal relation, but are less convincing, mostly because of incomplete documentation of symptoms or the possible attenuation of symptoms by medical intervention.

[e]The evidence derives from studies of diphtheria-tetanus toxoid for pediatric use (DT). If the evidence favors rejection of a causal relation between DT and encephalopathy, then in the committee's judgment the evidence favors rejection of a causal relation between Td and tetanus toxoid and encephalopathy.

[f]Infantile spasms and SIDS occur only in an age group that receives DT but not Td or tetanus toxoid.

[g]The evidence derives mostly from DPT. Because there are supportive data favoring rejection of a causal relation between DT and SIDS as well, if the evidence favors rejection of a causal relation between DPT and SIDS, then in the committee's judgment the evidence favors rejection of a causal relation between DT and SIDS.

[h]The evidence derives from tetanus toxoid. If the evidence favors acceptance of (or establishes) a causal relation between tetanus toxoid and an adverse event, then in the committee's judgment the evidence favors acceptance of (or establishes) a causal relation between DT and Td and the adverse event as well.

[i]The data come primarily from individuals proven to be immunocompromised.

# Afterword on Research Needs

In the course of its review, the committee found many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. Such shortcomings relate, for example, to pathologic mechanisms of specific infectious agents, the molecular basis of vaccine injury, and the natural history of conditions such as encephalopathy, mental retardation, and chronic arthritis. Many of the reports of case series suffer from inadequate or inconsistent case definitions, variable details about cases, inclusion of nonrepresentative case groups, and failure to consider potential confounding variables or biases. In addition, existing surveillance systems of vaccine injury have limited capacity to provide persuasive evidence of causation. Many of the population-based epidemiologic studies are too small or have inadequate lengths of follow-up to have a reasonable chance of detecting true adverse effects, unless these effects are large or occur promptly and consistently after vaccination. If research capacity and accomplishment in this field are not improved, future reviews of vaccine safety will be similarly handicapped.

The committee found few experimental studies published in relation to the number of epidemiologic studies published. As noted in Chapter 2, withholding of vaccines can be regarded as unethical. Although the committee was not charged with, and has not attempted, full consideration of the kinds of studies that would be both ethical and especially informative, either in the areas of vaccines that it has been charged to study or more



From IOM, 1991



generally, it recognizes, nevertheless, that opportunities may exist for informative experiments in human populations that take advantage of the possibility of using alternative schedules for administration of vaccines.

A careful review is needed to identify what sorts of questions might be best answered by further investigations and which kinds of studies could be carried out economically. The availability and introduction of new forms of pertussis vaccine, for example, could offer valuable opportunities for comparison of vaccine safety as well as efficacy. The committee is not in a position to make specific recommendations, but its experience points to fresh possibilities and to the need for such a review.

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# 11

# Need for Research and Surveillance

The lack of adequate data regarding many of the adverse events under study was of major concern to the committee. Presentations at public meetings indicated that many parents and physicians share this concern. Although the committee was not charged with proposing specific research investigations, in the course of its reviews additional obvious needs for research and surveillance were identified, and those are briefly described here.

## DIPHTHERIA AND TETANUS TOXOIDS

Recent advances in molecular analysis of diphtheria and tetanus toxins make it possible to construct mutant toxins that would be potentially safer, more immunogenic, and more readily purified for use as vaccines. A nontoxic variant of diphtheria toxin ($CRM_{197}$) is already used as a protein carrier molecule in one of the licensed *Haemophilus influenzae* type b polysaccharide-protein conjugate vaccines (see Chapter 9). If mutant toxin vaccines are more immunogenic than the presently used chemically inactivated toxins, successful immunization might be achieved with fewer doses and fewer adverse events.

The possibility of lot-specific reactions to diphtheria and tetanus toxoids, as has been demonstrated for diphtheria and tetanus toxoids and pertussis vaccine preparations, suggests that studies could be more revealing if the vaccines were tracked by lot.



From IOM, 1993

## MEASLES AND MUMPS VACCINES

Understanding the molecular basis for the risk of aseptic meningitis er immunization with the Urabe mumps strain (compared to the experi- :e with the Jeryl Lynn strain) might lead to better understanding of the :hogenetic capacity of mumps virus and to principles of viral pathogen- s that would aid in the development of safe attenuated virus vaccines in future.

Insulin-dependent diabetes mellitus (IDDM) is a serious and relatively nmon disorder. The large number of reports raising the suspicion that mps vaccine might induce the onset of IDDM suggests the need for tematic study of the question.

## POLIO VACCINES

There is a need to understand the basis for reversion of oral polio cine to a more virulent form to prevent its occurrence.

## HEPATITIS B VACCINES

Evidence is inadequate to accept or reject a causal relation between itis B vaccine and Guillain-Barré syndrome, transverse myelitis, optic itis, multiple sclerosis, or other demyelinating syndromes. The absence eports of such outcomes in large-scale field trials suggests that if hepati- 3 vaccine causes these adverse events, it does so at a very low fre- ıcy. Nevertheless, the number of reports questioning the relation be- n hepatitis B vaccine to one or the other of these disorders of similar acter suggests the need for systematic research.

The possibility that hepatitis B vaccine can cause an exacerbation of matoid arthritis should be carefully evaluated in a population-based /.

## GUILLAIN BARRÉ SYNDROME

The committee found that the evidence favors acceptance of a causal on between tetanus toxoid and Guillain-Barré syndrome (GBS) and :en oral polio vaccine and GBS. For the other vaccines, the associa- vith GBS is inconclusive, and research is needed to clarify the associa- The following information is potentially obtainable through research: he background incidence of GBS in the U.S. by year of life in the tric age group, particularly in infants and preschool-age children; (2) cidence of GBS after the receipt of each vaccine and combination of ıes administered to children or adults; and (3) more precise knowledge



of the mechanisms and sequence of events that result in vaccine-induced GBS.

## DEATH

The committee encourages active and aggressive follow-up of the reports to passive surveillance system of death in association with immunization. This follow-up should be timely and might include elements such as medical records, laboratory tests, and autopsy results. See the section on General Surveillance and Epidemiologic Studies for elaboration.

## SIMULTANEOUS ADMINISTRATION OF MORE THAN ONE VACCINE

The committee was able to identify little information pertaining to the risk of serious adverse events following administration of multiple vaccines simultaneously. This is an issue of increasing concern as more vaccines and vaccine combinations are developed for routine use. Both pre- and postmarketing research should address the issue.

## RISK-MODIFYING FACTORS

The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not. When it is clear that a vaccine can cause a specific adverse event, research should be encouraged to elucidate the factors that put certain people at risk for that adverse reaction.

## GENERAL SURVEILLANCE AND EPIDEMIOLOGIC STUDIES

Postmarketing surveillance of licensed vaccines in the United States depends upon voluntary reporting. Large numbers of alleged adverse events are reported to the Vaccine Adverse Event Reporting System (VAERS) of the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration. The committee found, however, that follow-up of serious adverse events was often incomplete, and the reported event was often not confirmed because of insufficient clinical, laboratory, or pathologic data. The committee suggests that, in the least, research should be conducted on the performance of passive reporting systems like VAERS. What is the quality and completeness of the information supplied? Can the reports received be used to estimate the true risk of vaccine-induced adverse events? Perhaps most important, how well does the surveillance system detect new

adverse events, events not previously reported in the medical literature demonstrated in epidemiologic studies?

The committee encourages the consideration of a more active system. Such a system might follow a representative sample of new vaccine recipients rather than the population at large. Alternatively, a randomly selected subgroup of serious adverse events reported to VAERS might be investigated fully. This latter approach suffers the inevitable limitations of retrospective review. It may be necessary to retain some broad-based passive reporting system to serve an early-warning function for unpredicted adverse events.

The committee found that a judgment regarding causality was often limited by the absence of background data for the occurrence of the pathologic condition (the putative adverse event) in apparently normal individuals not recently exposed to the vaccine. Regional or national disease registries could be established for those rare but serious conditions suspected of sometimes being caused by one or more licensed vaccines, for example, GBS, transverse myelitis, optic neuritis, and Stevens-Johnson syndrome. Such disease registries, if reasonably complete, would provide information about the descriptive epidemiology of these conditions, including age-, sex-, and race-specific background incidence rates. This information would facilitate the performance of case-control studies and other attempts to investigate vaccines as potential causes of the disorders.

The committee believes that future clinical trials of vaccines licensed or under development should study the serious adverse events examined by the present committee and its predecessor committee. Although any single trial may be too small to detect an effect of vaccine on rare adverse events, meta-analyses of several large trials may provide useful information. Meta-analysis could also be used to improve the statistical power of case-control studies to detect rare sequelae of vaccine administration.

With the existence of the large databases that have recently been established for defined populations, cohort studies become a feasible and desirable epidemiologic method of detecting the adverse effects of vaccines. Cohort studies would also permit the follow-up of patients exposed to specific vaccine types or batches that are suspected (e.g., on the basis of case reports) of being associated with a pathologic condition. Here, too, meta-analyses of cohort studies from different settings and different databases may permit identification of effects not detectable within individual studies.

Appendix 9



# APPENDIX A Status of Vaccines Under Development, 1995

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Bordetella pertussis* | *B. pertussis* surface protein expressed by vector (Salmonella) | ✓ | ✓ | | | | | | | + | | + |
| | Inactivated, nontoxic, PT vaccine | ✓ | ✓ | ✓ | ✓ | ✓ | | + | + | | | + |
| | PT recombinant vaccine | ✓ | ✓ | ✓ | ✓ | | ✓ | | | | | |
| | Purified PT and FHA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | | + |
| | Purified PT, FHA, pertactin, agglutinogen 2 and 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | | + |
| | Purified PT, FHA, pertactin, | ✓ | ✓ | ✓ | ✓ | | | | + | | | + |
| | Recombinant PT, FHA pertactin | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | PT peptides–CRM conjugates | ✓ | ✓ | | | | | | + | | | + |
| | Purified adenylate cyclase | ✓ | ✓ | | | | | | + | | | + |
| | DTaP–Hib conjugate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | | + |
| | [DTP–Hib conjugate–HBV] | ✓ | ✓ | ✓ | | | | | | | | |
| | [DTP–IPV] | ✓ | ✓ | ✓ | | | | | | | | |
| | DTP–Hib conjugate– IPV–HBV | ✓ | ✓ | ✓ | | | | | | | | |
| | DTaP–Hib conjugate–HBV | ✓ | ✓ | | | | | | | | | |
| | DTP, DTaP–IPV | ✓ | ✓ | | | | | | | | | |
| | DTaP–Hib conjugate–IPV–HBV | ✓ | ✓ | | | | | | | | | |
| *Blastomyces Dermatitidis* | Purified Yeast cell proteins (WI-1) | ✓ | ✓ | | | | | | | | | |
| *Borrelia burgdoferi* | Killed whole cell (canine use) | | | | | | ✓ | | | | | |
| | Purified Osp A | ✓ | ✓ | ✓ | ✓ | ✓ | | | + | | | |
| | BCG-expressed Osp A | ✓ | ✓ | | | | | | | + | | |
| | Purified Osp B, Osp C | ✓ | ✓ | | | | | | | | | |
| *Brugia malayi* | Purified parasite antigens (paramyosin, etc.) | ✓ | ✓ | | | | | + | + | + | + | |
| *Chlamydia* sp. | Subunit, major outer membrane protein (MOMP) | ✓ | ✓ | | | | | + | + | + | + | + |
| | Purified MOMP peptide | ✓ | ✓ | | | | | | | | | |
| | Polio construct | ✓ | ✓ | | | | | | | | | |
| | Heat-shock protein | ✓ | ✓ | | | | | | | | | |
| *Clostridium tetani* | Recombinant toxin | ✓ | | | | | | | | + | | |
| *Coccidioides immitis* | Formalin-killed spherules | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Recombinant 7.3 kD protein | ✓ | ✓ | | | | | | | | | |
| | Spherule homogenete (27kxg) | ✓ | ✓ | | | | | | | | | |
| | 33kD protein | ✓ | ✓ | | | | | | | | | |
| | DNA vaccine (7.3 kD protein in pc DNA3 | ✓ | ✓ | | | | | | | | | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Corynebacterium diphtheriae* | Recombinant toxin | ✓ | | | | | | | | | | | |
| *Cryptococcus neoformans* | Partially purified capsular polysaccharide | ✓ | ✓ | | | | | | | | | | |
| | Glycoconjugate of capsular polysaccharide with tetanus toxoid | ✓ | ✓ | | | | | | | | | | |
| Cytomegalovirus | Live, attenuated strains | ✓ | | ✓ | | | | | | | | | |
| | Glycoprotein subunit vaccine | ✓ | ✓ | ✓ | | | | | | | | | |
| | Multiprotein subunit vaccine | ✓ | | | | | | | | | | | |
| | Nucleic acid (DNA) vaccines | ✓ | | | | | | | | | | | |
| Dengue virus | Purified rDNA-expressed viral proteins | ✓ | ✓ | | | | | | | + | + | | |
| | Infectious clone | ✓ | ✓ | | | | | | | | | | |
| | Chimeric virus | ✓ | ✓ | | | | | | | | + | | |
| | Vaccinia vector (live) | ✓ | ✓ | | | | | | | | + | | |
| | Vaccinia Subunit | ✓ | ✓ | | | | | | | | + | | |
| | Baculovirus subunit | ✓ | ✓ | | | | | | | + | | | |
| | Synthetic peptide | ✓ | ✓ | | | | | | | + | | | |
| | Micelle/ISCOM | ✓ | ✓ | | | | | | + | + | | | |
| | Yeast Subunit | ✓ | | | | | | | | | | | |
| | Live, attenuated dengue virus | ✓ | ✓ | ✓ | | | | | | | | | |
| *Entamoeba histolytica* | Yeast subunit | ✓ | ✓ | | | | | | + | | + | + | |
| Enterotoxigenic *Escherichia coli* (ETEC) | Nontoxigenic ETEC derivative, live, attenuated | ✓ | ✓ | ✓ | ✓ | | | | | | | + | |
| | Subunit synthetic toxoid (ST) and B subunit of heat labile toxin (LT) | ✓ | ✓ | | | | | | + | + | + | + | |
| | Killed cell + B subunit of cholera toxin | ✓ | ✓ | ✓ | ✓ | | | | | | | + | |
| | Subunit, fusion protein LT and ST | ✓ | ✓ | | | | | | + | + | | + | |
| Epstein-Barr virus (EBV) | Glycoprotein subunit (gp350) | ✓ | ✓ | ✓ | | | | | | | + | | |
| | Vaccinia recombinant virus expressing gp350 | ✓ | | ✓ | | | | | | | + | | |
| | Peptide induction of CTL | ✓ | | ✓ | | | | | | | | + | |
| Group A Streptococcus | M protein/peptides linked to toxin subunit carriers | ✓ | ✓ | | | | | | | + | + | | |
| | M protein epitopes expressed in commensal vectors (S. gordonii) | ✓ | ✓ | | | | | | | | + | + | + |
| | Tetravalent hybrid constructs of M proteins | ✓ | ✓ | | | | | | | + | | | |
| | M peptides linked to toxin subunit carrier | ✓ | ✓ | ✓ | | | | | | + | | | |
| | M protein expressed in bacterial vector | ✓ | ✓ | ✓ | ✓ | | | | | | + | + | |
| | Multivalent M peptide hybrid constructs | ✓ | ✓ | ✓ | | | | | | + | | | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group B Streptococcus | Glycoconjugate vaccines of type Ia, Ib, II, III and V linked to a carrier protein | ✓ | ✓ | ✓ | ✓ | | | | + | | + | + |
| *Haemophilus influenzae* (nontypable) | Protein subunit containing P1, P2, and P6 proteins | ✓ | ✓ | | | | | | + | | + | |
| *Haemophilus influenzae* type b (Hib) | Glycoconjugate of Hib PRP with CRM197 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | + | + |
| | Glycoconjugate of Hib PRP with diphtheria toxoid | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | + | + |
| | Glycoconjugate of Hib PRP with tetanus toxoid | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | + | + |
| | Glycoconjugate of Hib PRP with Meningococcal type B outer membrane protein (OMP) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | + | + |
| Hepatitis A virus (HAV) | Inactivated HAV particles SmithKline Beecham Biologicals | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | |
| | Inactivated HAV particles,Merck Sharp & Dohme | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Inactivated HAV particles, Pasteur Merieux Serums et Vaccins, S.A. | ✓ | ✓ | ✓ | | | | | | | | |
| | Live, attenuated HAV | ✓ | ✓ | ✓ | ✓ | | | | + | + | | |
| | Viral proteins expressed by vectors, (baculovirus or vaccinia virus) | ✓ | ✓ | | | | | | + | + | | |
| Hepatitis B virus (HBV) | HBV core protein expressed by rDNA | ✓ | ✓ | | | | | | + | + | | |
| | HBV proteins expressed in yeast cells by rDNA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | + | + | + | | |
| | Salmonella vector | ✓ | ✓ | ✓ | | | | | | + | + | |
| | Variants | ✓ | ✓ | | | | | | | | | |
| | Generation of cytotoxic T lymphocytes (CTL) | ✓ | ✓ | ✓ | ✓ | | | | | | | |
| | DNA Vaccines | ✓ | ✓ | | | | | | | | | |
| | Plants | ✓ | ✓ | | | | | | | | | |
| Hepatitis C virus (HCV) | rDNA-expressed surface proteins and epitopes | ✓ | ✓ | | | | | | | | | |
| | Generation of cytotoxic T lymphocytes (CTL) | ✓ | ✓ | | | | | | | | | |
| | Nucleocapsid | ✓ | ✓ | | | | | | | | | |
| Hepatitis D virus | Synthetic peptides | ✓ | ✓ | | | | | | | | | |
| | Baculovirus | ✓ | | | | | | | | | + | |
| Hepatitis E virus | Expressed proteins | ✓ | ✓ | | | | | | | | | |
| Herpes simplex virus types 1 and 2 | Attenuated/recombinant | ✓ | ✓ | ✓ | | | | | | | | + |
| | Subunit | ✓ | ✓ | | | | | + | + | + | | |
| | Extract | ✓ | ✓ | ✓ | | | | | + | | | |
| | gD/recombinant | ✓ | ✓ | ✓ | ✓ | | | | + | + | + | |
| | gD/gB | ✓ | ✓ | | | | | | + | + | + | |
| | Vaccinia vectored proteins glycoproteins | ✓ | ✓ | | | | | | | | | |
| | Defective virus particle | ✓ | | | | | | | | | | |
| | DNA Vaccines | ✓ | ✓ | | | | | | | | | |
| | Replication of defective viruses | ✓ | ✓ | | | | | | | | | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Histoplasma capsulatum* | Purified yeast cell proteins (e.g., His-62) | ✓ | ✓ | | | | | | | | | |
| | Recombinant 6.2 lab protein (HS 60) | ✓ | ✓ | | | | | | | | | |
| Human immune deficiency virus HIV-1 | rgp 160/LAI (insect cells) | ✓ | | ✓ | | | | | | | | |
| | rgp 160/LAI (mammalian cells) | ✓ | ✓ | ✓ | | | | | + | + | | |
| | rgp 160/MN (mammalian cells) | ✓ | | ✓ | | | | | + | + | | |
| | rgp 120/SF2 (yeast) | ✓ | ✓ | ✓ | | | | | + | | | |
| | rgp 120/SF2 (mammalian cells) | ✓ | ✓ | ✓ | ✓ | | | | + | | | |
| | rgp 120/LAI (mammalian cells) | ✓ | ✓ | ✓ | | | | | | | | |
| | rgp 120/MN (mammalian cells) | ✓ | ✓ | ✓ | ✓ | | | | | | | |
| | M8V envelope neutralizing domain (V-3)-PPD conjugate (MN strain) | ✓ | | ✓ | | | | | | | | |
| | V-3-PPD conjugate (7strains) | ✓ | | ✓ | | | | | | | | |
| | V-3 - toxin A conjugate (MN strain) | ✓ | | ✓ | | | | | | | | |
| | V-3 peptides (MN strain) | ✓ | ✓ | ✓ | | | | | + | | | |
| | V-3 peptides (mixed strains) | ✓ | ✓ | ✓ | | | | | | | | |
| | V-3 lysine octapeptide (MN strain) | ✓ | ✓ | ✓ | | | | | | | | |
| | V-3 lysine octapeptide (15 strains) | ✓ | ✓ | ✓ | | | | | | | | |
| | V-3 lysine octapeptide (microparticulate) | ✓ | ✓ | ✓ | | | | + | | | + | |
| | Ty-V-3, virus-like particle | ✓ | ✓ | | | | | | + | | | |
| | V-3-T-helper epitope conjugate (CLTB-36) | ✓ | ✓ | ✓ | | | | | + | | | |
| | V-3-BCG recombinant | ✓ | ✓ | | | | | | | + | + | |
| | V-3-mycobacterium conjugate | ✓ | ✓ | | | | | | + | | | |
| | V-3-HBcAg particles | | | | | | | | | | | |
| | V-3-rhinovirus recombinant | ✓ | ✓ | | | | | | + | + | | |
| | V-3-mengovirus recombinant | ✓ | | | | | | | | + | | |
| | Lipidated gag peptide | ✓ | ✓ | ✓ | | | | | + | | | |
| | HGP-30 p17 gag peptide | ✓ | | ✓ | | | | | + | | | |
| | Ty-p24 virus-like particle | ✓ | ✓ | ✓ | | | | | | + | | |
| | rp24 | ✓ | ✓ | ✓ | | | | | | | | |
| | Inactivated HIV-1 | ✓ | ✓ | ✓ | | | | | | | | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Human Immune Deficiency Virus HIV-1 continued | HIV-1 pseudovirions | | ✓ | ✓ | | | | | | | + | | |
| | HIV-gag V-3 virus like particles | | ✓ | ✓ | | | | | | | | | |
| | Vaccinia/HIV-1 envelope | | ✓ | ✓ | ✓ | | | | | | + | | |
| | Vaccinia/HIV-1 gag-pol, envelope (env) | | ✓ | ✓ | ✓ | | | | | | + | | |
| | Highly attenuated vaccinia, HIV env, gag-pol | | ✓ | ✓ | | | | | | | + | | |
| | Canary pox/HIV-1 env | | ✓ | ✓ | ✓ | | | | | | + | | |
| | Canary pox/HIV-1 gag-protease, env | | ✓ | ✓ | ✓ | | | | | | + | | |
| | Adenovirus/HIV-1 env | | ✓ | ✓ | | | | | | | + | + | |
| | Poliovirus/HIV-1 gag-pol, env | | ✓ | ✓ | | | | | | | + | + | |
| | Mengovirus/HIV-1 nef | | ✓ | | | | | | | | + | | |
| | Salmonella/HIV-1 gag, or env, or nef | | ✓ | | | | | | | | + | + | |
| | BCG/HIV-1 env | | ✓ | ✓ | | | | | | | + | | |
| | V3-Shigella recombinant | | ✓ | ✓ | | | | | | | + | + | |
| | V3-Lactococcus recombinant | | ✓ | ✓ | | | | | | | + | + | |
| | V3-HGP30 p17 peptide conjugate with cholera toxin | | ✓ | ✓ | | | | | | + | | | |
| | rpg 120 in liposomes, with cholera toxin | | ✓ | ✓ | | | | | | + | | | |
| | HIV-1 DNA vaccines | | ✓ | ✓ | | | | | | | | | |
| Human Immune Deficiency Virus, HIV-2 | Inactivated HIV-2 | | ✓ | ✓ | | | | | | + | | | |
| | rgp 130 (purified from virion) | | ✓ | ✓ | | | | | | + | | | |
| | rgp 160 (insect cells) | | ✓ | ✓ | | | | | | | + | | |
| | Highly attenuated, vaccinia HIV-2 gag-pol env | | ✓ | ✓ | | | | | | | + | | |
| | Vaccinia HIV-2 env | | ✓ | ✓ | | | | | | | + | | |
| | Canary pox HIV-2 gag-pol env | | ✓ | ✓ | | | | | | | + | | |
| | Salmonella HIV-2 env, gag | | ✓ | ✓ | | | | | | | + | | |
| Human papillomavirus | Capsid protein | | ✓ | ✓ | | | | | | | | | |
| Influenza virus | Cold-adapted live, attenuated | | ✓ | ✓ | ✓ | ✓ | ✓ | | | + | | + | + |
| | Purified viral HA subunit | | ✓ | ✓ | ✓ | | | | + | + | + | + | |
| | Liposome containing viral HA | | ✓ | ✓ | ✓ | | | | + | + | | + | |
| | Purified CTL specific peptides | | ✓ | ✓ | ✓ | | | | + | + | | + | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Influenza virus continued | Microencapsulated inactivated vaccine | ✓ | ✓ | ✓ | | | | + | + | | + | |
| | Purified, inactivated viral neuraminidase | ✓ | ✓ | ✓ | | | | + | + | | + | |
| | Baculovirus expressed recombinant HA subunit | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Baculovirus expressed nucleoprotein | ✓ | ✓ | ✓ | | | | | | | | |
| | Transfection with nucleic acid (DNA) plasmid expressing HA subunit | ✓ | ✓ | | | | | + | + | | | |
| Japanese B encephalitis virus | Whole, inactivated virus particles | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | + | + | | | |
| | Infectious clone | ✓ | ✓ | | | | | | | | | |
| | Purified DNA expressed protein | ✓ | ✓ | | | | | + | | + | | |
| | Live attenuated virus | ✓ | ✓ | | | | | | | | | |
| | Vaccinia vector (live) | ✓ | ✓ | | | | | | | + | | |
| *Legionella pneumophila* | Attenuated mutant | ✓ | ✓ | | | | | | | | | |
| | Purified bacterial surface protein | ✓ | ✓ | | | | | | | | | |
| *Leishmania sp.* | Attenuated or killed whole parasites | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Leishmanial surface antigens (gp63, 6 kD, and lipophosphoglycan) | ✓ | ✓ | | | | | | | | + | |
| Measles virus | rDNA HA and fusion proteins | ✓ | ✓ | | | | | + | + | + | + | |
| | Live, attenuated | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | | |
| | High titer live (multiple strains) | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Poxvirus vector (live) | ✓ | ✓ | ✓ | | | | | + | | + | |
| *Moraxella catarrhalis* | High molecular weight, outer membrane protein | ✓ | | | | | | | | | | |
| *Mycobacterium leprae* | BCG plus purified *M. leprae* antigens (35 kD) | ✓ | | | | | | | | | | |
| | Recombinant antigens in BCG | | | | | | | | | + | | |
| | Live BCG expressing *M. leprae* antigens | ✓ | ✓ | | | | | | | + | + | |
| | BCG plus heatkilled *M. leprae* | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Mycobacterium leprae* continued | Heat-killed, purified *M. leprae* | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Live, cross-reacting atypical mycobacteria | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| *Mycobacterium tuberculosis* | BCG plus purified *M. tuberculosis* antigens | ✓ | ✓ | | | | | | | | | |
| | T cell reactive immunogens | ✓ | | | | | | | | | | |
| | Recombinant antigens in BCG | ✓ | ✓ | | | | | | | + | | |
| | *M. vaccae* | ✓ | | ✓ | | | | | + | | | |
| *Mycoplasma pneumoniae* | Recombinant membrane associated proteins | ✓ | ✓ | | | | | | + | + | + | |
| | Purified outer membrane protein | ✓ | ✓ | | | | | | | | | |
| *Neisseria gonorrheae* | Purified protein subunit containing OMP P.1 | ✓ | ✓ | | | | | + | | | + | + |
| | Protein I | ✓ | | | | | | | | | | |
| | Purified/PIII mutant | ✓ | ✓ | | | | | | | | | |
| | Chimera/recombinant | ✓ | ✓ | | | | | | | | | |
| | Iron-binding protein | ✓ | ✓ | | | | | | | | | |
| *Neisseria meningitidis* A and C | Several glycoconjugates | ✓ | ✓ | ✓ | | | | | | + | + | |
| *Neisseria meningitidis B* | Glycoconjugate plus N.meningitidis protein antigens | ✓ | ✓ | ✓ | | | | | | + | + | |
| Parainfluenza virus | Cold-adapted PIV3 attenuated virus | ✓ | ✓ | ✓ | ✓ | | | | | | | + |
| | Purified HN and F protein subunit vaccine | ✓ | ✓ | ✓ | | | | | | + | + | |
| | *Bovine attenuated* | ✓ | ✓ | ✓ | ✓ | | | | | | | + |
| | Microencapsulated vaccine | ✓ | ✓ | | | | | | + | | | + |
| | Recombinant/chimeric HNF | ✓ | ✓ | | | | | | | | + | |
| *Plasmodium* spp. | Circumsporozoite antigen expressed in several vectors | ✓ | ✓ | ✓ | ✓ | | | | + | + | + | + |
| | Gametocyte antigens | ✓ | ✓ | ✓ | | | | | + | + | + | |
| | Blood stage antigens | ✓ | ✓ | ✓ | ✓ | ✓ | | | + | + | + | |
| | Circumsporozoite (CS) antigen | ✓ | ✓ | ✓ | ✓ | | | | + | + | + | + |
| | Non-CS pre-erythrocytic antigens | ✓ | ✓ | | | | | | + | + | + | |



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| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Plasmodium* spp. continued | Blood stage antigens | | ✓ | ✓ | ✓ | ✓ | ✓ | | + | + | + | | |
| | Gametocyte antigens | | ✓ | ✓ | ✓ | | | | + | + | + | | |
| | Combination vaccines incorporating different stage specific antigens | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | + | | |
| Poliovirus | Reversion-stable attenuated OPV | | ✓ | | | | | | | | | + | |
| | Live, attenuated (oral) | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | + | + | |
| | Inactivated | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | + | |
| | Live (nonreverting) | | ✓ | ✓ | | | | | | | | + | |
| | Chimeric virus | | ✓ | ✓ | | | | | | + | + | + | |
| | Enhanced potency inactivated | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | + | + | + | + | + |
| *Pseudomonas aeruginosa* and *Pseudomona cepacia* | Purified bacterial proteins, including flagellar Ag, LPS-O, porins, several inactivated bacterial toxins, and high m.w. polysaccharide antigen and glycoconjugate | | ✓ | ✓ | ✓ | | | | + | | | + | + |
| Rabies virus | rDNA vaccinia virus recombinant for use in sylvatic rabies (veterinary vaccine) | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| | Inactivated mammalian brain | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | |
| | Inactivated cell culture | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | |
| Respiratory syncytial virus | Live, attenuated *ts* and/or *ca* strains | | ✓ | ✓ | ✓ | | | | | | | + | |
| | Purified, F protein | | ✓ | ✓ | ✓ | ✓ | | | | + | | | + |
| *Rickettsia rickettsii* | Subunit vaccine containing major surface proteins (155 and 120 kD) | | ✓ | ✓ | | | | | | | | | |
| Rotavirus | Attenuated human/rhesus reassortant viruses | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | + | |
| | Attenuated human rotavirus (cold-adapted) | | ✓ | ✓ | ✓ | | | | | | | + | |
| | *Salmonella* expressing VP4, VP7, or both | | ✓ | ✓ | | | | | | + | + | + | |
| | Attenuated bovine/human virus reassortants (WC3) | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | + | |
| | Human nursery strains | | ✓ | ✓ | ✓ | ✓ | | | | | | + | |
| | Purified rotavirus proteins rDNA-derived virus-like particles (VLPs) | | ✓ | ✓ | | | | | + | | + | + | |
| | Vaccinia virus recombinant expressing VP4, VP7, or both | | ✓ | ✓ | | | | | | + | | + | |
| | DNA vaccines | | ✓ | ✓ | | | | | | | | | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rubella virus | Live, attenuated | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | + | | | + |
| | Infectious clone | ✓ | | | | | | | | | | + |
| | Synthetic peptide | ✓ | | | | | | | + | | | |
| *Salmonella typhi* | Vi carbohydrate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | + | + | + | | |
| | Vi carbohydrate-protein conjugate | ✓ | ✓ | ✓ | | | | + | + | + | | |
| | Live, attenuated Ty21a vaccine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | + | |
| | Live, attenuated auxotrophic mutants | ✓ | ✓ | ✓ | ✓ | | | + | + | + | + | |
| *Schistosoma mansoni* | Purified larval antigens | ✓ | ✓ | | | | | | | | | |
| | Recombinant larval antigens | ✓ | ✓ | | | | | + | | + | + | |
| *Shigella* (all species) | Polysaccharide-protein conjugate | ✓ | ✓ | ✓ | ✓ | | | | | | | |
| *Shigella dysenteriae* | Live auxotrophic, attenuated mutants | ✓ | ✓ | | | | | | | + | + | |
| *Shigella flexneri/sonnei* | *E. coli* hybrids | ✓ | ✓ | ✓ | ✓ | | | | | + | + | |
| *Streptococcus pneumoniae* | Glycoconjugate vaccine (4, 6B, 9N, 14, 18C, 19F, 23F) conjugated to meningococcal B OMP | ✓ | ✓ | ✓ | ✓ | ✓ | | + | + | | + | + |
| | Glycoconjugate vaccine (6B, 14, 19, 23F) conjugated to tetanus toxoid | ✓ | ✓ | ✓ | ✓ | | | | | | | |
| | Glycoconjugate vaccine (6B, 14, 18C, 19F) conjugated to CRM 197 | ✓ | ✓ | ✓ | ✓ | | | + | + | | + | + |
| | Glycoconjugate vaccine (1,5,6B, 14, 18C, 19F, 23F) conjugated to CRM 197 | ✓ | ✓ | | | | | | | | | |
| *Toxoplasma gondii* | Purified parasite antigen (p30) | ✓ | ✓ | | | | | + | | | | |
| | Live, attenuated parasites | ✓ | ✓ | | | | | | | | | |
| *Treponema pallidum* | Surface lipoproteins | ✓ | ✓ | | | | | | | | | |
| | Antiidiotype/fibronectin | ✓ | ✓ | | | | | | | | | |
| Varicella zoster virus | Live, attenuated vaccine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | |
| | Subunit, glycoproteins | ✓ | | | | | | | | | + | |
| | Vaccinia vectored glycoprotein | ✓ | | | | | | | | | + | |
| | Ty-vectored glycoprotein | ✓ | | | | | | | | | + | |

| Target Agent | Vaccine Approaches | Basic R&D | Animal Model | Phase I Studies | Phase II Studies | Phase III Studies | Licensed Vaccine | Delivery Vehicles | Immune Enhance | Vector/Carrier | Mucosal Immunity | Maternal Immunity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venezuelan equine encephalitis, eastern equine encephalitis, and western equine encephalitis | Inactivated, whole virus particles | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| Venezuelan equine encephalitis | Live, attenuated virus strains | ✓ | ✓ | | | | | | | | | |
| | Infectious clones | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | |
| *Vibrio cholerae* | Killed bacteria plus toxin B subunit | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | + | |
| | Live, recombinant O1 | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | + | |
| | Live recombinant O139 | ✓ | ✓ | ✓ | ✓ | | | | | | + | |
| | Conjugate lipopolysaccharide (LPS) | ✓ | ✓ | | | | | | | | | |
| Yellow fever virus | Live attenuated | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | |
| | Infectious clone | ✓ | ✓ | | | | | | | | | |

Keys to Interpreting this Table

A mark (✓) indicates that studies are being done - or are about to be done - at the stage indicated; this does not necessarily mean that tests have been completed at that stage. Licensure applies to use in the United States.

A mark (+) in the columns to the right of the veritcal bold line indicates approaches that are being examined in the development of a given candidate vaccine, They include:

Delivery Vehicles - This includes the use of biodegradable microparticles or timed-release methodologies for the delivery of a vaccine.

Immune Enhancement - Indicates that various means are being explored to enhance the immune response to a given vaccine; this includes the use of immunological adjuvants or other immunomodulators.

Vector/Carrier - Indicates that a vector is being used, either for the production of recombinant antigen (expression vector) or as a carrier for the *in vivo* expression of antigen.

Mucosal Immunization - Indicates that approaches are being considered which favor the development of a mucosal immune response (mucosal immunity).

Maternal Immunization - Indicates that a vaccine is being evaluated for use in pregnant females to confer protective immunity in the newborn.

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